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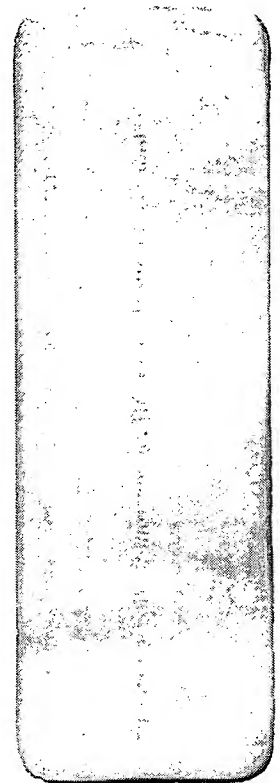
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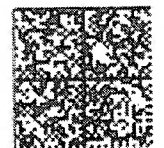
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/925,188	08/09/2001	Jean Ackermann	20739	4231

151 7590 05/05/2004

HOFFMANN-LA ROCHE INC.
PATENT LAW DEPARTMENT
340 KINGSLAND STREET
NUTLEY, NJ 07110

EXAMINER

ROBINSON, BINTA M

ART UNIT	PAPER NUMBER
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1625

DATE MAILED: 05/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/925,188

Applicant(s)

ACKERMANN ET AL.

Examiner

Binta M. Robinson

Art Unit

1625

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3,4,6-17,21,22,24-30,34-45 and 63-98 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1,3,4,6-17,21,22,24-30,34-45 and 63-98 is/are rejected.
- 7) ☒ Claim(s) 93 is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date ____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: ____.

Detailed Action

Claims 1, 3-4, 6-17, 21-22, 24-30, 34-45, 63-98 are now pending.

The examiner appreciates the applicant's narrowing of the claims to the elected subject matter of Group IV which reads on the compound of formula I where V is -CH₂-, -CH=CH- or alkynyl, A1-A4 do not contain a carbon ring, and all other variables are as recited, a pharmaceutical composition, and a process of preparing compounds of formula I. However, the claims are not allowable as is, because new rejections have been found.

(new rejections)

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3, 4, 6, 7, 8-17, 21, 22, 24-30, 34-45, 63-92, 94, 95, 96, 97, 98 provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16-22 of copending Application No. 2003/0186984 A1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent application claims a genus that encompasses the subgenus of instant compounds and pharmaceutical compositions containing.

Application No. 2003/0186984 A1 et. al. teaches the instant compound as shown in Formula I, wherein U is O or a lone pair, V is $-\text{CH}=\text{CH}-$ or alkynyl, m and n independently from each other are 0 to 7 and m+n is 0 to 7, o is 0, A1 is hydrogen, lower-alkyl, hydroxy-lower-alkyl, or lower alkenyl, A2 is lower-alkyl, cycloalkyl, cyclylalkyl-lower-alkyl, or lower-alkenyl, optionally substituted by R1, A3 and A4 independently from each other are hydrogen or lower-alkyl or A5 is hydrogen, lower-alkyl, or lower-alkenyl, A6 is pyridinyl, pyridazinyl, pyrimidinyl or pyrazinyl, r1 is hydroxy, hydroxy-lower-alkyl, lower-alkoxy, loweralkoxy carbonyl, N(R3R4) or thio-loweralkoxy, R3 and R4 independently from each other are hydrogen or lower-alkyl. At column 32, see the compound of formula I and the radicals defined. The difference between the prior art compound and the instantly claimed compounds and the pharmaceutical compositions containing them is that the instant compounds are a subgenus of the genus of Application No. 2003/0186984 compounds. It would have been obvious to one of ordinary skill in the art to select various known radicals within a genus to prepare structurally similar compounds. For instance, see claim 32, where a disclosed species is exemplified. Accordingly, the compounds are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds over those of the generic prior art compounds.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1, 3, 37, 39, 41, 42, 43, 44, 66, 68, 69, 70, 71, 73, -75, 77, 78, 82, 86, 87-88, 90-92, 95, 97 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claim 1, line 8, page 3 and all other occurrences throughout claims 3, 37, 39, 41, 42, 43, 44, 66, 68, 69, 70, 71, 73, -75, 77, 78, 82, 86, 87-88, 90-92, 95, 97, the phrase "and pharmaceutically acceptable esters of the compounds of formula I" is ambiguous. Esters of the compounds of formula I are not the same species as the compound of formula I. What Esters of the compounds of formula I is the applicant claiming? Additionally, these claims are compound claims simultaneously making a claim to one compound and then more than one compound. However, a compound claim can only claim one compound at a time, because a compound can only consist of one compound at a time. However, a mixture or composition consists of at least two compounds. Is the applicant claiming a composition or a compound in these claims?

B. Claim 1 recites the limitation "V is O or S" in line 9, page 2 of the amendment filed 2/20/04. There is insufficient antecedent basis for this limitation in the claim.

Claims 93 is objected to for being based on rejected claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Binta M. Robinson whose telephone number is (571) 272-0692. The examiner can normally be reached on M-F (9:30-6:00).

Art Unit: 1625

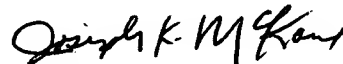
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703)308-4242, (703)305-3592, and (703)305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)-272-1600.



BMR



JOSEPH K. MCKANE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Notice of References Cited	Application/Control No. 09/925,188	Applicant(s)/Patent Under Reexamination ACKERMANN ET AL.	
	Examiner Binta M. Robinson	Art Unit 1625	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
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FOREIGN PATENT DOCUMENTS

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	N					
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	Q					
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	S					
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NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	US Patent Application 2003/0186984 A1, "Substituted Cyclohexane Derivatives", October 2, 2003, Ackermann et. al.
	V	
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	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.



US 20030186984A1

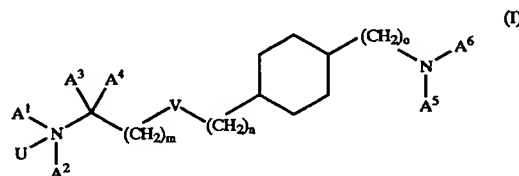
(19) **United States**(12) **Patent Application Publication** (10) **Pub. No.: US 2003/0186984 A1**
Ackermann et al. (43) **Pub. Date: Oct. 2, 2003**(54) **SUBSTITUTED CYCLOHEXANE
DERIVATIVES**(52) **U.S. Cl. 514/247; 514/275; 514/255.06;
514/352; 544/224; 544/322;
544/407; 546/304**(76) **Inventors: Jean Ackermann, Riehen (CH);
Johannes Aebi, Basle (CH); Henrietta
Dehmlow, Grenzach-Wyhlen (DE);
Hans-Peter Maerki, Basle (CH);
Olivier Morand, Hegenheim (FR)**(57) **ABSTRACT**

Correspondence Address:
**HOFFMANN-LA ROCHE INC.
PATENT LAW DEPARTMENT
340 KINGSLAND STREET
NUTLEY, NJ 07110**

The present invention relates to compounds of formula (I)

(21) **Appl. No.: 10/310,559**(22) **Filed: Dec. 5, 2002**(30) **Foreign Application Priority Data**

Dec. 20, 2001 (EP) 01130284.1

Publication Classification(51) **Int. Cl.⁷ A61K 31/505; A61K 31/4965;
C07D 241/02; C07D 239/02;
C07D 213/72**

wherein A^1 , A^2 , A^3 , A^4 , A^5 , A^6 , U, V, m, n and o are as defined in the specification, and pharmaceutically acceptable salts thereof. The compounds are useful for the treatment and/or prophylaxis of diseases which are associated with the 2,3-oxidosqualene-lanosterol cyclase biosynthetic pathway such as hypercholesterolemia and hyperlipemia.

SUBSTITUTED CYCLOHEXANE DERIVATIVES

BACKGROUND OF THE INVENTION

[0001] 2,3-oxidosqualene-lanosterol cyclase (EC 5.4.99.) is required for the biosynthesis of cholesterol, ergosterol and other sterols. Causal risk factors that directly promote the development of coronary and peripheral atherosclerosis include elevated low-density lipoprotein cholesterol (LDL-C), low high-density lipoprotein cholesterol (HDL-C), hypertension, cigarette smoking and diabetes mellitus. Other synergistic risk factors include elevated concentrations of triglyceride (TG)-rich lipoproteins, small, dense low-density lipoprotein particles, lipoprotein (a) (Lp(a)), and homocysteine. Predisposing risk factors modify the causal or conditional risk factors and thus affect atherogenesis indirectly. The predisposing risk factors are obesity, physical inactivity, family history of premature CVD, and male sex. The strong connection between coronary heart disease (CHD) and high LDL-C levels in plasma, and the therapeutic advantage of lowering elevated LDL-C levels are now well established (Gotto et al., *Circulation* 81, 1990, 1721-1733; Stein et al., *Nutr. Metab. Cardiovasc. Dis.* 2, 1992, 113-156; Illingworth, *Med. Clin. North. Am.* 84, 2000, 23-42). Cholesterol-rich, sometimes unstable, atherosclerotic plaques lead to the occlusion of blood vessels resulting in an ischemia or an infarct. Studies with respect to primary prophylaxis have shown that a lowering of plasma LDL-C levels in plasma reduces the frequency of non-fatal incidences of CHD, while the overall morbidity remains unchanged. The lowering of plasma LDL-C levels in patients with pre-established CHD (secondary intervention) reduces CHD mortality and morbidity; meta-analysis of different studies shows that this decrease is proportional to the reduction of the LDL-C (Ross et al., *Arch. Intern. Med.* 159, 1999, 1793-1802).

[0002] The clinical advantage of cholesterol lowering is greater for patients with pre-established CHD than for asymptomatic persons with hypercholesterolemia. According to current guidelines, cholesterol lowering treatment is recommended for patients who had survived a myocardial infarct or patients suffering from angina pectoris or another atherosclerotic disease, with a target LDL-C level of 100 mg/dl.

[0003] Preparations such as bile acid sequestrants, fibrates, nicotinic acid, probucol as well as statins, i.e. HMG-Co-A reductase inhibitors such as simvastatin and atorvastatin, are used for usual standard therapies. The best statins reduce plasma LDL-C effectively by at least 40%, and also plasma triglycerides, a synergistic risk factor, but less effectively. In contrast, fibrates reduce plasma triglycerides effectively, but not LDL-C. Combination of a statin and a fibrate proved to be very efficacious in lowering LDL-C and triglycerides (Ellen and McPherson, *J. Cardiol.* 81, 1998, 60B-65B), but safety of such a combination remains an issue (Shepherd, *Eur. Heart J.* 16, 1995, 5-13). A single drug with a mixed profile combining effective lowering of both LDL-C and triglycerides would provide additional clinical benefit to asymptomatic and symptomatic patients.

[0004] In humans, statins are well tolerated at standard dosage, but reductions in non-sterol intermediates in the cholesterol synthesis pathway, such as isoprenoids and coenzyme Q, may be associated with adverse clinical events at

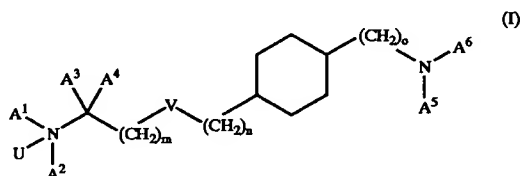
high doses (Davignon et al., *Can. J. Cardiol.* 8, 1992, 843-864; Pederson and Tobert, *Drug Safety* 14, 1996, 11-24).

[0005] This has stimulated the search for, and development of compounds that inhibit cholesterol biosynthesis, yet act distal to the synthesis of these important, non-sterol intermediates. 2,3-oxidosqualene:lanosterol cyclase (OSC), a microsomal enzyme, represents a unique target for a cholesterol-lowering drug (Morand et al., *J. Lipid Res.*, 38, 1997, 373-390; Mark et al., *J. Lipid Res.* 37, 1996, 148-158). OSC is downstream of farnesyl-pyrophosphate, beyond the synthesis of isoprenoids and coenzyme Q. In hamsters, pharmacologically active doses of an OSC inhibitor showed no adverse side-effects, in contrast to a statin which reduced food-intake and body weight, and increased plasma bilirubin, liver weight and liver triglyceride content (Morand et al., *J. Lipid Res.*, 38, 1997, 373-390). The compounds described in European Patent Application No. 636 367, which inhibit OSC and which lower the total cholesterol in plasma, belong to these substances.

[0006] OSC inhibition does not trigger the overexpression of HMGR because of an indirect, negative feed-back regulatory mechanism involving the production of 24(S),25-epoxycholesterol (Peffley et al., *Biochem. Pharmacol.* 56, 1998, 439-449; Nelson et al., *J. Biol. Chem.* 256, 1981, 1067-1068; Spencer et al., *J. Biol. Chem.* 260, 1985, 13391-13394; Panini et al., *J. Lipid Res.* 27, 1986, 1190-1204; Ness et al., *Arch. Biochem. Biophys.* 308, 1994, 420-425). This negative feed-back regulatory mechanism is fundamental to the concept of OSC inhibition because (i) it potentiates synergistically the primary inhibitory effect with an indirect down-regulation of HMGR, and (ii) it prevents the massive accumulation of the precursor monooxidosqualene in the liver. In addition, 24(S),25-epoxycholesterol was found to be one of the most potent agonists of the nuclear receptor LXR (Janowski et al., *Proc. Natl. Acad. Sci. USA*, 96, 1999, 266-271). Considering that 24(S),25-epoxycholesterol is a by-product of inhibition of OSC it is hypothesized that the OSC inhibitors of the present invention could also indirectly activate LXR-dependent pathways such as (i) cholesterol-7 α -hydroxylase to increase the consumption of cholesterol via the bile acid route, (ii) expression of ABC proteins with the potential to stimulate reverse cholesterol transport and increase plasma HDL-C levels (Venkateswaran et al., *J. Biol. Chem.* 275, 2000, 14700-14707; Costet et al., *J. Biol. Chem.* June 2000, in press; Ordovas, *Nutr. Rev.* 58, 2000, 76-79; Schmitz and Kaminsky, *Front. Biosci.* 6, 2001, D505-D514), and/or inhibit intestinal cholesterol absorption (Mangelsdorf, XIIth International Symposium on Atherosclerosis, Stockholm, June 2000). In addition, possible cross talks between fatty acid and cholesterol metabolism mediated by liver LXR have been hypothesized (Tobin et al., *Mol. Endocrinol.* 14, 2000, 741-752).

SUMMARY OF THE INVENTION

[0007] The present invention is concerned with novel cyclohexane derivatives, their manufacture and their use as medicaments. In particular, the invention relates to compounds of the formula (I)



[0008] wherein

[0009] U is O or a lone pair,

[0010] V is a single bond, O, S, $-\text{CH}-\text{CH}-\text{CH}_2-$, $-\text{O}-$, $-\text{CH}=\text{CH}-$, or $-\text{C}=\text{C}-$,

[0011] m and n independently from each other are 0 to 7 and m+n is 0 to 7, with the proviso that m is not 0 if V is O or S,

[0012] is 0 to 2

[0013] A¹ is hydrogen, lower-alkyl, hydroxy-lower-alkyl, or lower-alkenyl,

[0014] A² is lower-alkyl, cycloalkyl, cycloalkyl-lower-alkyl, or lower-alkenyl, optionally substituted by R¹, or

[0015] A¹ and A² are bonded to each other to form a ring and $-\text{A}^1-\text{A}^2-$ is lower-alkylene or lower-alkenylene, optionally substituted by R¹, in which one $-\text{CH}_2-$ group of $-\text{A}^1-\text{A}^2-$ can optionally be replaced by NR², S, or O,

[0016] A³ and A⁴ independently from each other are hydrogen or lower-alkyl, or

[0017] A³ and A⁴ are bonded to each other to form a ring together with the carbon atom to which they are attached and $-\text{A}^3-\text{A}^4-$ is $-(\text{CH}_2)_{2-5}-$,

[0018] A⁵ is hydrogen, lower-alkyl, or lower-alkenyl,

[0019] A⁶ is pyridinyl, pyridazinyl, pyrimidinyl or pyrazinyl, optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower-alkyl, lower-alkyl-cycloalkyl, thio-lower-alkoxy, cycloalkyl, carbamoyl, carboxy, carboxy-lower-alkyl, cyano, amino, mono- and dialkylamino, lower-alkoxy, lower-alkoxy-lower-alkyl, lower-alkoxy-carbonyl, lower-alkoxy-carbonyl-lower-alkyl, lower-alkenyl, lower-alkynyl, aryl, aryl-lower-alkyl, aryloxy, halogen, heteroaryl, heterocyclyl, heterocyclyl-lower-alkyl and trifluoromethyl,

[0020] R¹ is hydroxy, hydroxy-lower-alkyl, lower-alkoxy, lower-alkoxycarbonyl, halogen, CN, N(R³, R⁴), or thio-lower-alkoxy,

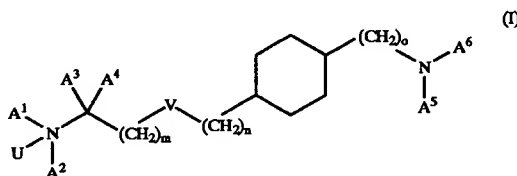
[0021] R², R³, and R⁴ independently from each other are hydrogen or lower-alkyl,

[0022] and pharmaceutically acceptable salts thereof, with the proviso, that the compound of formula (I) is not trans-[4-(2-Dipropylamino-ethyl)-cyclohexyl]-pyrimidin-2-yl-amine.

[0023] The compounds of the present invention are useful for the treatment and/or prophylaxis of diseases associated with 2,3-oxidosqualene-lanosterol cyclase such as hypercholesterolemia and hyperlipemia.

DETAILED DESCRIPTION OF THE INVENTION

[0024] In detail, the present invention relates to compounds of formula (I)



[0025] wherein

[0026] U is O or a lone pair,

[0027] V is a single bond, O, S, $-\text{CH}=\text{CH}-\text{CH}_2-$, $-\text{O}-$, $-\text{CH}=\text{CH}-$, or $-\text{C}=\text{C}-$,

[0028] m and n independently from each other are 0 to 7 and m+n is 0 to 7, with the proviso that m is not 0 if V is O or S,

[0029] is 0 to 2

[0030] A¹ is hydrogen, lower-alkyl, hydroxy-lower-alkyl, or lower-alkenyl,

[0031] A² is lower-alkyl, cycloalkyl, cycloalkyl-lower-alkyl, or lower-alkenyl, optionally substituted by R¹, or

[0032] A¹ and A² are bonded to each other to form a ring and $-\text{A}^1-\text{A}^2-$ is lower-alkylene or lower-alkenylene, optionally substituted by R¹, in which one $-\text{CH}_2-$ group of $-\text{A}^1-\text{A}^2-$ can optionally be replaced by NR², S, or O,

[0033] A³ and A⁴ independently from each other are hydrogen or lower-alkyl, or

[0034] A³ and A⁴ are bonded to each other to form a ring together with the carbon atom to which they are attached and $-\text{A}^3-\text{A}^4-$ is $-(\text{CH}_2)_{2-5}-$,

[0035] A⁵ is hydrogen, lower-alkyl, or lower-alkenyl,

[0036] A⁶ is pyridinyl, pyridazinyl, pyrimidinyl or pyrazinyl, optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower-alkyl, lower-alkyl-cycloalkyl, thio-lower-alkoxy, cycloalkyl, carbamoyl, carboxy, carboxy-lower-alkyl, cyano, amino, mono- and dialkylamino, lower-alkoxy, lower-alkoxy-lower-alkyl, lower-alkoxy-carbonyl, lower-alkoxy-carbonyl-lower-alkyl, lower-alkenyl, lower-alkynyl, aryl, aryl-lower-alkyl, aryloxy, halogen, heteroaryl, heterocyclyl, heterocyclyl-lower-alkyl and trifluoromethyl,

[0037] R^1 is hydroxy, hydroxy-lower-alkyl, lower-alkoxy, lower-alkoxycarbonyl, halogen, CN, $N(R^3, R^4)$, or thio-lower-alkoxy,

[0038] R^2, R^3 , and R^4 independently from each other are hydrogen or lower-alkyl, and pharmaceutically acceptable salts thereof, with the proviso, that the compound of formula (I) is not trans-[4-(2-Dipropylamino-ethyl)-cyclohexyl]-pyrimidin-2-yl-amine.

[0039] The present compounds of formula I inhibit OSC and therefore also inhibit the biosynthesis of cholesterol, ergosterol and other sterols, and reduce the plasma cholesterol levels. They can therefore be used in the therapy and prophylaxis of hypercholesterolemia, hyperlipemia, arteriosclerosis and vascular diseases in general. Furthermore, they can be used in the therapy and/or prevention of mycoses, parasite infections, gallstones, cholestatic liver disorders, tumors and hyperproliferative disorders, e.g. hyperproliferative skin and vascular disorders. In addition, it has unexpectedly been found that the compounds of the present invention can also be of therapeutical use to improve glucose tolerance in order to treat and/or prevent related diseases such as diabetes. The compounds of the present invention further exhibit improved pharmacological properties compared to known compounds.

[0040] Unless otherwise indicated, the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

[0041] In this specification the term "lower" is used to mean a group consisting of one to seven, preferably of one to four carbon atom(s).

[0042] The term "lone pair" refers to an unbound electron pair, in particular to the unbound electron pair of a nitrogen atom in e.g. an amine.

[0043] The term "halogen" refers to fluorine, chlorine, bromine and iodine, with fluorine, chlorine and bromine being preferred.

[0044] The term "alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of one to twenty carbon atoms, preferably one to sixteen carbon atoms, more preferably one to ten carbon atoms.

[0045] Lower-alkyl groups as described below also are preferred alkyl groups.

[0046] The term "lower-alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent alkyl radical of one to seven carbon atoms, preferably one to four carbon atoms. This term is further exemplified by such radicals as methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl, t-butyl and the like.

[0047] The term "cycloalkyl" refers to a monovalent carbocyclic radical of 3 to 10 carbon atoms, preferably 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

[0048] The term "alkoxy" refers to the group $R'-O-$, wherein R' is an alkyl. The term "lower-alkoxy" refers to the group $R'-O-$, wherein R' is a lower-alkyl. The term "thio-alkoxy" refers to the group $R'-S-$, wherein R' is an

alkyl. The term "thio-lower-alkoxy" refers to the group $R'-S-$, wherein R' is a lower-alkyl.

[0049] The term "alkenyl", alone or in combination with other groups, stands for a straight-chain or branched hydrocarbon residue comprising an olefinic bond and up to 20, preferably up to 16 carbon atoms, more preferably up to 10 carbon atoms. Lower-alkenyl groups as described below also are preferred alkenyl groups. The term "lower-alkenyl" refers to a straight-chain or branched hydrocarbon residue comprising an olefinic bond and up to 7, preferably up to 4 carbon atoms, such as e.g. 2-propenyl.

[0050] The term "alkynyl", alone or in combination with other groups, stands for a straight-chain or branched hydrocarbon residue comprising a triple bond and up to 20, preferably up to 16 carbon atoms, more preferably up to 10 carbon atoms. Lower-alkynyl groups as described below also are preferred alkynyl groups. The term "lower-alkynyl" refers to a straight-chain or branched hydrocarbon residue comprising a triple bond and up to 7, preferably up to 4 carbon atoms, such as e.g. 2-propynyl.

[0051] The term "alkylene" refers to a straight chain or branched divalent saturated aliphatic hydrocarbon group of 1 to 20 carbon atoms, preferably 1 to 16 carbon atoms, more preferably up to 10 carbon atoms. Lower-alkylene groups as described below also are preferred alkylene groups. The term "lower-alkylene" refers to a straight chain or branched divalent saturated aliphatic hydrocarbon group of 1 to 7, preferably 1 to 6 or 3 to 6 carbon atoms. Straight chain alkylene or lower-alkylene groups are preferred.

[0052] The term "alkenylene" refers to a straight chain or branched divalent hydrocarbon group comprising an olefinic bond and up to 20 carbon atoms, preferably up to 16 carbon atoms, more preferably up to 10 carbon atoms. Lower-alkenylene groups as described below also are preferred alkenylene groups. The term "lower-alkenylene" refers to a straight chain or branched divalent hydrocarbon group comprising an olefinic bond and up to 7, preferably up to 5, C-atoms. Straight chain alkenylene or lower-alkenylene groups are preferred.

[0053] The term "aryl" relates to the phenyl or naphthyl group, preferably the phenyl group, which can optionally be substituted by 1 to 3 substituents independently selected from the group consisting of lower-alkyl, lower-alkenyl, lower-alkynyl, dioxo-lower-alkylene (forming e.g. a benzo-dioxyl group), halogen, hydroxy, CN, CF_3 , NH_2 , $N(H, lower-alkyl)$, $N(lower-alkyl)_2$, aminocarbonyl, carboxy, NO_2 , lower-alkoxy, thio-lower-alkoxy, lower-alkylcarbonyl, lower-alkylcarbonyloxy, lower-alkoxycarbonyl. Preferred substituents are halogen, CF_3 , CN, lower-alkyl and/or lower-alkoxy.

[0054] The term "heteroaryl" refers to an aromatic 5- or 6-membered ring which can comprise 1, 2 or 3 atoms selected from nitrogen, oxygen and/or sulphur, such as furyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, thienyl, isoxazolyl, oxazolyl, imidazolyl, or pyrrolyl. A heteroaryl group may have a substitution pattern as described earlier in connection with the term "aryl".

[0055] The term "heterocyclyl" as used herein denotes non-aromatic monocyclic heterocycles with 5 or 6 ring members, which comprise 1, 2 or 3 hetero atoms selected from nitrogen, oxygen and sulfur. Examples of suitable

heterocycles are pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolyl, pyrazolidinyl, pyrazolyl, piperidyl, piperazinyl, morpholinyl, pyranyl, 4,5-dihydro-oxazolyl, 4,5-dihydro-thiazolyl. A heterocyclyl group may have a substitution pattern as described earlier in connection with the term "aryl".

[0056] The term "pharmaceutically acceptable salts" embraces salts of the compounds of formula (I) with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, fumaric acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like, which are non toxic to living organisms. Preferred salts are phosphates, citrates, fumarates, formates, hydrochlorides, hydrobromides and methanesulfonic acid salts.

[0057] Preferred are compounds of formula (I) and/or pharmaceutically acceptable salts thereof. Other preferred embodiments relate to compounds of formula (I) wherein U is a lone pair or to compounds of formula (I) wherein U is O.

[0058] Compounds of formula (I) as described above, in which V is a single bond, O, $-\text{CH}=\text{CH}-\text{CH}_2-\text{O}-$, or $-\text{C}=\text{C}-$ relate to a preferred embodiment of the present invention. More preferred compounds as defined above are those, wherein V is $-\text{C}=\text{C}-$.

[0059] In a further preferred embodiment of the present invention, m is 0 to 3, more preferably m is 0. Compounds of formula (I), in which n is 0 or 1 are also preferred, with those compounds wherein n is 0 being more preferred. Compounds as described above, in which the number of carbon atoms of $(\text{CH}_2)_m$, V and $(\text{CH}_2)_n$ together is 7 or less, are also preferred. Other preferred compounds of formula (I) as described above are those, wherein o is 0 or 1.

[0060] Other preferred compounds of the present invention are those in which A¹ represents lower-alkyl, preferably those in which A¹ is methyl or ethyl. Another group of preferred compounds of the present invention are those in which A² represents lower-alkenyl, or lower-alkyl optionally substituted by R², wherein R² is hydroxy or lower-alkoxy, with those compounds wherein A² represents methyl, propyl or 2-hydroxy-ethyl being especially preferred.

[0061] Compounds of formula (I), wherein A¹ and A² are bonded to each other to form a ring and $-\text{A}^1-\text{A}^2-$ is lower-alkylene are also preferred, with those compounds, wherein $-\text{A}^1-\text{A}^2-$ is $-(\text{CH}_2)_5-$ being especially preferred.

[0062] In compounds wherein A¹ and A² are bonded to each other to form a ring, said ring is preferably a 4-, 5-, or 6-membered ring such as e.g. piperidinyl or pyrrolidinyl. [0034] A further preferred embodiment of the present invention relates to compounds of formula (I), wherein A³ and A⁴ represent hydrogen.

[0063] Compounds of formula (I), wherein A is hydrogen or lower-alkyl also relate to a preferred embodiment of the present invention, with those compounds, wherein A⁵ is methyl relating to a particularly preferred embodiment. Other preferred compounds are those in which A⁶ is pyridinyl, pyridazinyl, pyrimidinyl or pyrazinyl, optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower-alkyl, lower-alkoxy, halogen,

pyridyl and thienyl. More preferred compounds of formula (I) are those wherein A⁶ is pyridazinyl or pyrimidinyl, optionally substituted with 1 or 2 substituents independently selected from the group consisting of bromo, chloro, ethyl and pyridyl, with those compounds wherein A⁶ is 5-bromo-pyrimidin-2-yl, 6-chloro-pyridazin-3-yl, 5-chloro-pyrimidin-2-yl, 5-pyridin-4-yl-pyrimidin-2-yl, 5-ethyl-pyrimidin-2-yl being particularly preferred.

[0064] Preferred compounds of general formula (I) are those selected from the group consisting of

[0065] Trans-{4-[3-(Allyl-methyl-amino)-prop-1-ynyl]-cyclohexyl}-(5-bromo-pyrimidin-2-yl)-methyl-amine,

[0066] Trans-(5-Bromo-pyrimidin-2-yl)-methyl-{4-[3-(methyl-propyl-amino)-prop-1-ynyl]-cyclohexyl}-amine,

[0067] Trans-(5-Bromo-pyrimidin-2-yl)-{4-(3-dimethylamino-prop-1-ynyl)-cyclohexyl}-methyl-amine,

[0068] Trans-(5-Bromo-pyrimidin-2-yl)-{4-[3-(ethyl-(2-methoxy-ethyl)-amino)-prop-1-ynyl]-cyclohexyl}-methyl-amine,

[0069] Trans-{4-[3-(Allyl-methyl-amino)-propyl]-cyclohexyl}-(5-bromo-pyrimidin-2-yl)-methyl-amine,

[0070] Trans-(5-Bromo-pyrimidin-2-yl)-methyl-{4-[3-(methyl-propyl-amino)-propyl]-cyclohexyl}-amine,

[0071] Trans-(5-Bromo-pyrimidin-2-yl)-{4-(3-dimethylamino-propyl)-cyclohexyl}-methyl-amine,

[0072] Trans-(5-Bromo-pyrimidin-2-yl)-{4-[3-(ethyl-(2-methoxy-ethyl)-amino)-propyl]-cyclohexyl}-methyl-amine,

[0073] Trans-{4-(3-Dimethylamino-prop-1-ynyl)-cyclohexyl}-methyl-pyrimidin-2-yl-amine,

[0074] Trans-(6-Chloro-pyridazin-3-yl)-{4-(3-dimethylamino-prop-1-ynyl)-cyclohexyl}-methyl-amine,

[0075] Trans-(5-Chloro-pyrimidin-2-yl)-{4-(3-dimethylamino-prop-1-ynyl)-cyclohexyl}-methyl-amine,

[0076] Trans-(5-Bromo-pyridin-2-yl)-{4-(3-dimethylamino-prop-1-ynyl)-cyclohexyl}-methyl-amine,

[0077] Trans-{4-(3-Dimethylamino-prop-1-ynyl)-cyclohexyl}-methyl-pyridin-2-yl-amine,

[0078] Trans-{4-(3-Dimethylamino-prop-1-ynyl)-cyclohexyl}-methyl-pyrazin-2-yl-amine,

[0079] trans-[2-[(3-{4-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-cyclohexyl}-prop-2-ynyl)-ethyl-amino]-ethanol],

[0080] trans-[(5-Bromo-pyrimidin-2-yl)-methyl-{4-(3-piperidin-1-yl-prop-1-ynyl)-cyclohexyl}-amine],

[0081] trans-[(5-Bromo-pyrimidin-2-yl)-{4-(3-diethylamino-prop-1-ynyl)-cyclohexyl}-methyl-amine],

[0082] Trans-2-[(3-{4-[(6-Chloro-pyridazin-3-yl)-methyl-amino]-cyclohexyl}-prop-2-ynyl)-ethyl-amino]-ethanol,

- [0083] Trans-2-[(3-{4-[(5-Chloro-pyrimidin-2-yl)-methyl-amino]-cyclohexyl}-prop-2-ynyl)-ethyl-amino]-ethanol,
- [0084] Trans-2-[(3-{4-[(5-Bromo-pyridin-2-yl)-methyl-amino]-cyclohexyl}-prop-2-ynyl)-ethyl-amino]-ethanol,
- [0085] trans-[4-(3-Dimethylamino-prop-1-ynyl)-cyclohexyl]-methyl-(5-pyridin-4-yl-pyrimidin-2-yl)-amine,
- [0086] trans-[4-(3-Dimethylamino-prop-1-ynyl)-cyclohexyl]-methyl-(5-thiophen-3-yl-pyrimidin-2-yl)-amine,
- [0087] Trans-6-(Methyl-{4-[3-(methyl-propyl-amino)-prop-1-ynyl]-cyclohexyl}-amino)-nicotinonitrile,
- [0088] Trans-6-{Methyl[4-(3-piperidin-1-yl-prop-1-ynyl)-cyclohexyl]-amino}-nicotinonitrile,
- [0089] Trans-6-[[4-(3-Dimethylamino-prop-1-ynyl)-cyclohexyl]-methyl-amino]-nicotinonitrile,
- [0090] Trans-(5-Ethyl-pyrimidin-2-yl)-methyl-[4-(3-piperidin-1-yl-prop-1-ynyl)-cyclohexyl]-amine,
- [0091] Trans-[4-(3-Dimethylamino-prop-1-ynyl)-cyclohexyl]-(5-ethyl-pyrimidin-2-yl)-methyl-amine,
- [0092] Trans-(5-Bromo-pyrimidin-2-yl)-[4-(4-dimethylamino-but-1-ynyl)-cyclohexyl]-methyl-amine,
- [0093] Trans-(6-Chloro-pyridazin-3-yl)-methyl-[4-(3-piperidin-1-yl-prop-1-ynyl)-cyclohexyl]-amine,
- [0094] Trans-(5-Chloro-pyrimidin-2-yl)-methyl-[4-(3-piperidin-1-yl-prop-1-ynyl)-cyclohexyl]-amine,
- [0095] Trans-(5-Bromo-pyrimidin-2-yl)-[4-(4-dimethylamino-butyl)-cyclohexyl]-methyl-amine,
- [0096] Trans-(5-Bromo-pyrimidin-2-yl)-[2-(4-dimethylaminomethyl-cyclohexyl)-ethyl]-amine,
- [0097] Trans-(5-Bromo-pyrimidin-2-yl)-methyl-[4-(4-piperidin-1-yl-but-1-ynyl)-cyclohexyl]-amine,
- [0098] Trans-(2E)-(5-Bromo-pyrimidin-2-yl)-[4-(4-dimethylamino-but-2-enyloxy)-cyclohexyl]-methyl-amine,
- [0099] Trans-(2E)-(5-Bromo-pyrimidin-2-yl)-methyl-[4-(4-piperidin-1-yl-but-2-enyloxy)-cyclohexyl]-amine,
- [0100] Trans-(6-Chloro-pyridazin-3-yl)-methyl-[4-(3-pyrrolidin-1-yl-prop-1-ynyl)-cyclohexyl]-amine,
- [0101] Trans-(5-Bromo-pyrimidin-2-yl)-methyl-[4-(4-piperidin-1-yl-butyl)-cyclohexyl]-amine,
- [0102] Trans-(5-Bromo-pyrimidin-2-yl)-[2-(4-piperidin-1-ylmethyl-cyclohexyl)-ethyl]-amine,
- [0103] Trans-(6-Chloro-pyridazin-3-yl)-methyl-{4-[3-(methyl-propyl-amino)-prop-1-ynyl]-cyclohexyl}-amine,
- [0104] Trans-(6-Chloro-pyridazin-3-yl)-[4-(3-diethylamino-prop-1-ynyl)-cyclohexyl]-methyl-amine,
- [0105] Trans-(6-Chloro-pyridazin-3-yl)-[4-(4-dimethylamino-but-2-ynyl)-cyclohexyl]-methyl-amine,
- [0106] Trans-(6-Chloro-pyridazin-3-yl)-methyl-[4-(4-piperidin-1-yl-but-2-ynyl)-cyclohexyl]-amine,
- [0107] Trans-(5-Bromo-pyrimidin-2-yl)-[4-(4-dimethylamino-but-2-ynyl)-cyclohexyl]-methyl-amine,
- [0108] Trans-(5-Bromo-pyrimidin-2-yl)-methyl-[4-(4-piperidin-1-yl-but-2-ynyl)-cyclohexyl]-amine,
- [0109] Trans-(5-Bromo-pyrimidin-2-yl)-methyl-[4-(2-pyrrolidin-1-yl-ethoxy)-cyclohexyl]-amine,
- [0110] Trans-(5-Bromo-pyrimidin-2-yl)-[2-(4-dimethylaminomethyl-cyclohexyl)-ethyl]-methyl-amine,
- [0111] Trans-(5-Bromo-pyrimidin-2-yl)-methyl-[2-(4-piperidin-1-ylmethyl-cyclohexyl)-ethyl]-amine,
- [0112] Trans-[4-(3-Dimethylamino-prop-1-ynyl)-cyclohexyl]-methyl-(6-methyl-pyridazin-3-yl)-amine,
- [0113] Trans-2-[Ethyl-(3-{4-[methyl-(6-methyl-pyridazin-3-yl)-amino]-cyclohexyl}-prop-2-ynyl)-amino]-ethanol,
- [0114] Trans-[4-(3-Dimethylamino-prop-1-ynyl)-cyclohexyl]-(6-methoxy-pyridazin-3-yl)-methyl-amine,
- [0115] trans-(5-Bromo-pyrimidin-2-yl)-[4-(3-dimethylamino-prop-1-ynyl)-cyclohexylmethyl]-methyl-amine,
- [0116] trans-2-[[3-(4-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl)-cyclohexyl]-prop-2-ynyl]-ethyl-amino]-ethanol,
- [0117] trans-(5-Bromo-pyrimidin-2-yl)-methyl-[4-(3-piperidin-1-yl-prop-1-ynyl)-cyclohexylmethyl]-amine,
- [0118] trans-[4-(3-Dimethylamino-prop-1-ynyl)-cyclohexylmethyl]-(5-ethyl-pyrimidin-2-yl)-methyl-amine,
- [0119] trans-2-{Ethyl-[3-(4-[(5-ethyl-pyrimidin-2-yl)-methyl-amino]-methyl)-cyclohexyl]-prop-2-ynyl]-amino}-ethanol,
- [0120] trans(5-Ethyl-pyrimidin-2-yl)-methyl-[4-(3-piperidin-1-yl-prop-1-ynyl)-cyclohexylmethyl]-amine,
- [0121] trans-(6-Chloro-pyridazin-3-yl)-[4-(3-dimethylamino-prop-1-ynyl)-cyclohexylmethyl]-methyl-amine,
- [0122] trans-2-[[3-(4-[(6-Chloro-pyridazin-3-yl)-methyl-amino]-methyl)-cyclohexyl]-prop-2-ynyl]-ethyl-amino]-ethanol,
- [0123] trans-(6-Chloro-pyridazin-3-yl)-methyl-[4-(3-piperidin-1-yl-prop-1-ynyl)-cyclohexylmethyl]-amine,
- [0124] trans-2-[(4-{2-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-ethyl}-cyclohexylmethyl)-ethyl-amino]-ethanol,
- [0125] trans-[4-(3-Dimethylamino-prop-1-ynyl)-cyclohexylmethyl]-methyl-(5-propyl-pyrimidin-2-yl)-amine,
- [0126] trans-2-{Ethyl-[3-(4-[(methyl-(5-propyl-pyrimidin-2-yl)-amino]-methyl)-cyclohexyl]-prop-2-ynyl]-amino}-ethanol,
- [0127] trans-(5-Chloro-pyrimidin-2-yl)-[4-(3-dimethylamino-prop-1-ynyl)-cyclohexylmethyl]-methyl-amine,

[0128] trans-2-[[3-(4-[(5-Chloro-pyrimidin-2-yl)-methyl-amino]-methyl)-cyclohexyl]-prop-2-ynyl]-ethyl-amino 1-ethanol,

[0129] trans-3-[(4-{2-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-ethyl}-cyclohexylmethyl)-amino]-propan-1-ol, and

[0130] trans-3-[(4-{2-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-ethyl}-cyclohexylmethyl)-methyl-amino]-propan-1-ol,

[0131] and pharmaceutically acceptable salts thereof.

[0132] Particularly preferred compounds of general formula (I) are those selected from the group consisting of

[0133] Trans-(5-Bromo-pyrimidin-2-yl)-methyl-[4-{3-(methyl-propyl-amino)-prop-1-ynyl}-cyclohexyl]-amine,

[0134] Trans-(5-Bromo-pyrimidin-2-yl)-[4-(3-dimethyl-amino-prop-1-ynyl)-cyclohexyl]-methyl-amine,

[0135] Trans-(6-Chloro-pyridazin-3-yl)-[4-(3-dimethyl-amino-prop-1-ynyl)-cyclohexyl]-methyl-amine,

[0136] Trans-(5-Chloro-pyrimidin-2-yl)-[4-(3-dimethyl-amino-prop-1-ynyl)-cyclohexyl]-methyl-amine,

[0137] Trans-[(5-Bromo-pyrimidin-2-yl)-methyl-[4-(3-piperidin-1-yl-prop-1-ynyl)-cyclohexyl]-amine],

[0138] Trans-[4-(3-Dimethyl-amino-prop-1-ynyl)-cyclohexyl]-methyl-(5-pyridin-4-yl-pyrimidin-2-yl)-amine,

[0139] Trans-[4-(3-Dimethyl-amino-prop-1-ynyl)-cyclohexyl]-[5-ethyl-pyrimidin-2-yl]-methyl-amine,

[0140] Trans-(5-Bromo-pyrimidin-2-yl)-[4-(3-dimethyl-amino-prop-1-ynyl)-cyclohexylmethyl]-methyl-amine,

[0141] Trans-2-[[3-(4-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl)-cyclohexyl]-prop-2-ynyl]-ethyl-amino}-ethanol,

[0142] Trans-2-{Ethyl-[3-(4-[(5-ethyl-pyrimidin-2-yl)-methyl-amino]-methyl)-cyclohexyl]-prop-2-ynyl]-amino}-ethanol,

[0143] Trans(5-Ethyl-pyrimidin-2-yl)-methyl-[4-(3-piperidin-1-yl-prop-1-ynyl)-cyclohexylmethyl]-amine, and

[0144] Trans-2-[[3-(4-[(6-Chloro-pyridazin-3-yl)-methyl-amino]-methyl)-cyclohexyl]-prop-2-ynyl]-ethyl-amino}-ethanol,

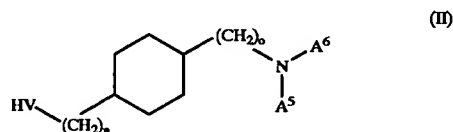
[0145] and pharmaceutically acceptable salts thereof

[0146] Compounds of formula (I) can have one or more asymmetric carbon atoms and can exist in the form of optically pure enantiomers or as racemates. They can exist as cis- or trans-isomers. The invention embraces all of these forms. Compounds of formula (I) which are trans-isomers (with reference to the cyclohexyl ring) are preferred.

[0147] It will be appreciated, that the compounds of general formula (I) in this invention may be derivatised at functional groups to provide derivatives which are capable of conversion back to the parent compound in vivo.

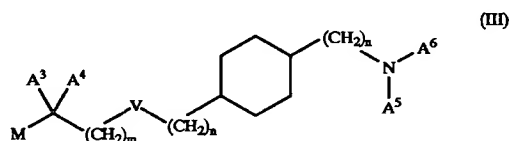
[0148] The present invention also relates to a process for the manufacture of compounds of formula (I) as described above, which process comprises

[0149] reacting a compound of formula (II)



[0150] with a compound $(A^1, A^2, U)N-C(A^3, A^4)-(CH_2)_m-M$, wherein V is O or S, M is mesylate, tosylate, triflate, Cl, Br or I, and U, A^1 , A^2 , A^3 , A^4 , A^5 , A^6 , m, n and o are as defined above, or wherein HV is mesylate, tosylate, triflate, Cl, Br or I, and M is OH, SH,

[0151] or b) reacting a compound of formula (III)



[0152] with a compound NHA^1A^2 , wherein M is mesylate, tosylate, triflate, Cl, Br or I, and A^1 , A^2 , A^3 , A^4 , A^5 , A^6 , V, m, n and o are as defined above,

[0153] and optionally converting a compound of formula (I) as defined above to a pharmaceutically acceptable salt,

[0154] and optionally converting a compound of formula (I) as defined above, wherein U is a lone pair, to a corresponding compound wherein U is O.

[0155] Reactions of a compound of formula (II) with a compound $(A^1, A^2, U)N-C(A^3, A^4)-(CH_2)_m-M$ can be carried out by procedures known in the art and described in Scheme 5 in a solvent like N,N-dimethylformamide, N,N-dimethylacetamide or nitromethane in the presence of a base like sodium hydride or 2,6-di-tert-butylpyridine in a temperature range of e.g. 0° C. to 80° C. Reactions of a compound of formula (III) with a compound NHA^1A^2 can be carried out by procedures known in the art and described in the examples preferentially in solvents like N,N-dimethylacetamide, N,N-dimethylformamide or methanol, preferentially between room temperature and 80° C. A compound as defined above can be converted to a pharmaceutically acceptable salt by procedures known in the art such as by a treatment with a corresponding acid in a solvent like ethanol, methanol or dichloromethane in a temperature range of e.g. -20° C. and +40° C. A compound as defined above, wherein U is a lone pair can be converted to a compound wherein U is O by procedures known in the art such as by reaction with a mixture of hydrogen peroxide urea adduct and phthalic anhydride in dichloromethane at room temperature.

[0156] The invention further relates to compounds of formula (I) as defined above, when manufactured according to a process as defined above.

[0157] As described above, the compounds of formula (I) of the present invention can be used for the treatment and/or prophylaxis of diseases which are associated with OSC such as hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, mycoses, parasite infections and gallstones, and/or treatment and/or prophylaxis of impaired glucose tolerance, diabetes, tumors and/or hyperproliferative disorders, preferably for the treatment and/or prophylaxis of hypercholesterolemia and/or hyperlipemia. Hyperproliferative skin and vascular disorders particularly come into consideration as hyperproliferative disorders.

[0158] The invention therefore also relates to pharmaceutical compositions comprising a compound as defined above and a pharmaceutically acceptable carrier and/or adjuvant.

[0159] Further, the invention relates to compounds as defined above for use as therapeutic active substances, particularly as therapeutic active substances for the treatment and/or prophylaxis of diseases which are associated with OSC such as hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, mycoses, parasite infections, gallstones, tumors and/or hyperproliferative disorders, and/or treatment and/or prophylaxis of impaired glucose tolerance and diabetes, preferably for the treatment and/or prophylaxis of hypercholesterolemia and/or hyperlipemia.

[0160] In another embodiment, the invention relates to a method for the treatment and/or prophylaxis of diseases which are associated with OSC such as hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, mycoses, parasite infections, gallstones, tumors and/or hyperproliferative disorders, and/or treatment and/or prophylaxis of impaired glucose tolerance and diabetes, preferably for the treatment and/or prophylaxis of hypercholesterolemia and/or hyperlipemia, which method comprises administering a compound as defined above to a human being or animal.

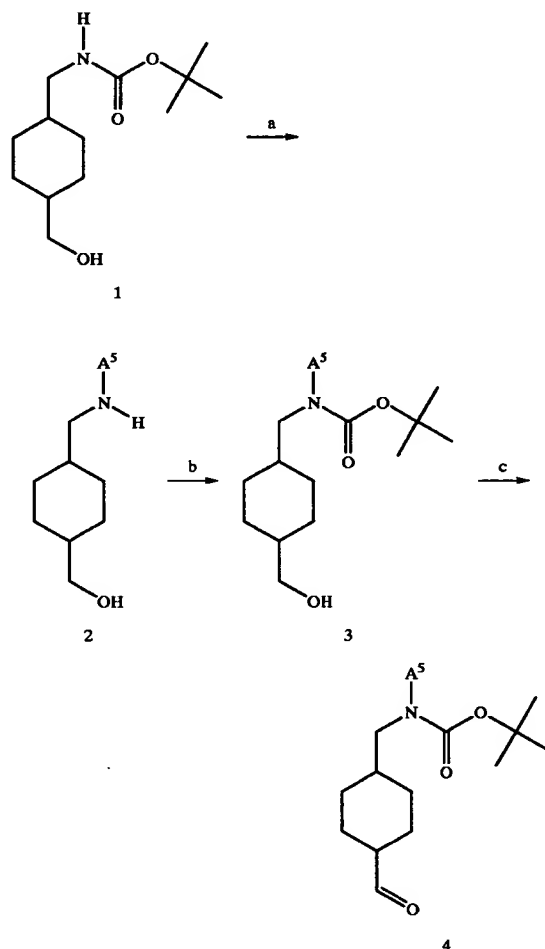
[0161] The invention further relates to the use of compounds as defined above for the treatment and/or prophylaxis of diseases which are associated with OSC such as hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, mycoses, parasite infections, gallstones, tumors and/or hyperproliferative disorders, and/or treatment and/or prophylaxis of impaired glucose tolerance and diabetes, preferably for the treatment and/or prophylaxis of hypercholesterolemia and/or hyperlipemia.

[0162] In addition, the invention relates to the use of compounds as defined above for the preparation of medicaments for the treatment and/or prophylaxis of diseases which are associated with OSC such as hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, mycoses, parasite infections, gallstones, tumors and/or hyperproliferative disorders, and/or treatment and/or prophylaxis of impaired glucose tolerance and diabetes, preferably for the treatment and/or prophylaxis of hypercholesterolemia and/or hyperlipemia. Such medicaments comprise a compound as defined above.

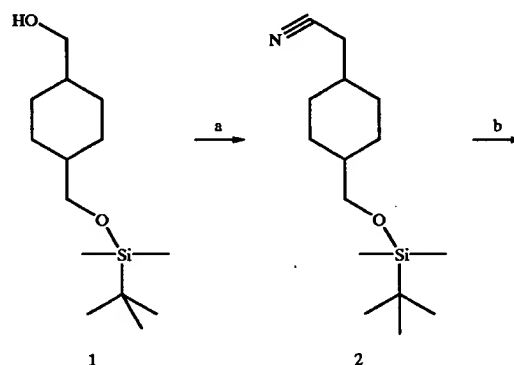
[0163] The compounds of formula (I) can be manufactured by the methods given below, by the methods given in the examples or by analogous methods. Appropriate reaction conditions for the individual reaction steps are known to the person skilled in the art. Starting materials are either commercially available or can be prepared by methods analo-

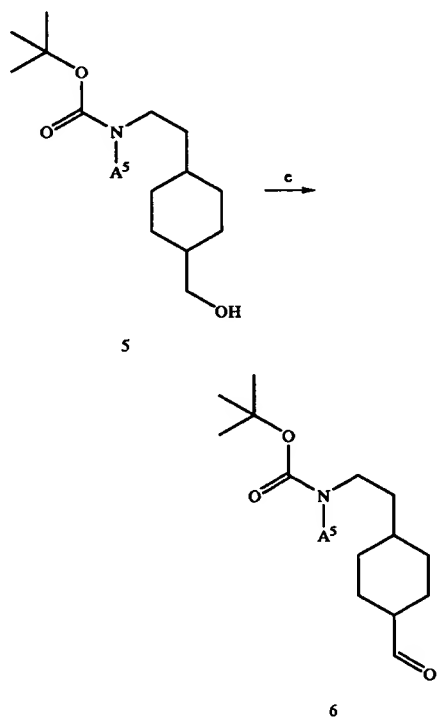
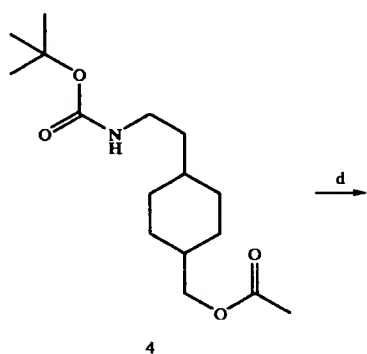
gous to the methods given below or in the examples or by methods known in the art.

Scheme 1

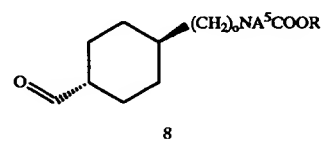
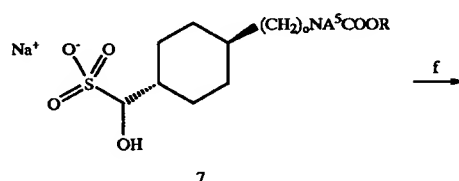
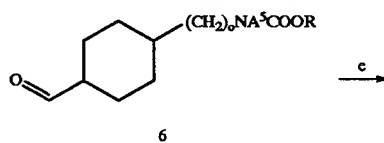
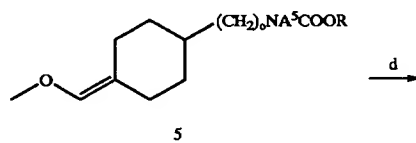
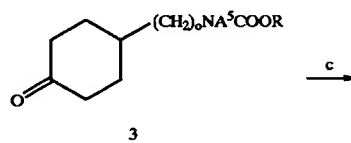
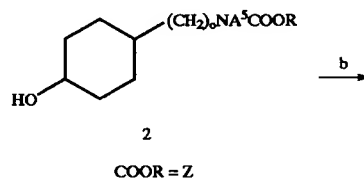
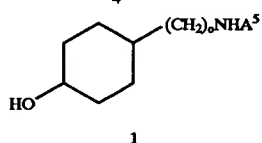
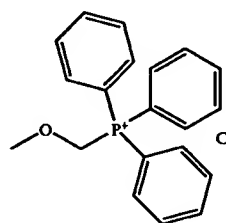


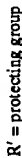
Scheme 2



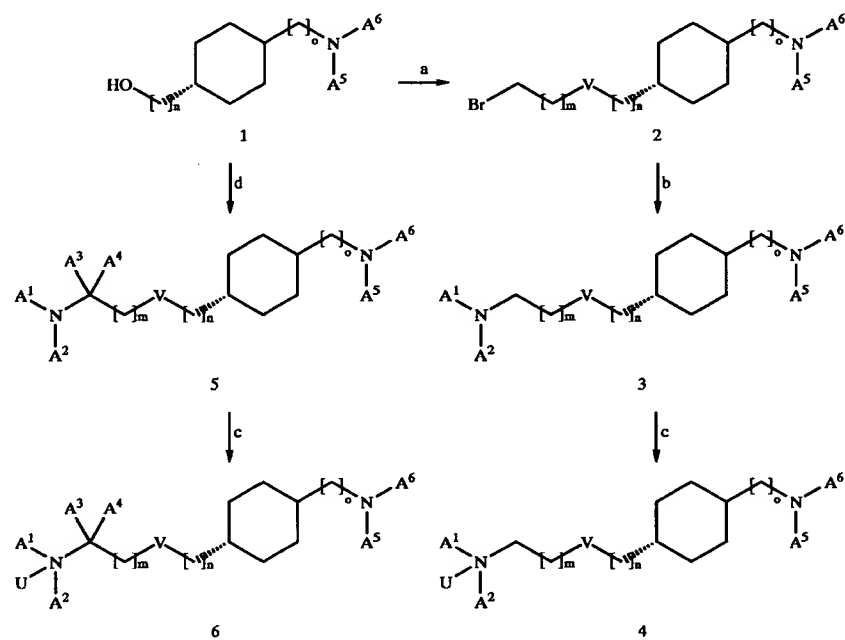


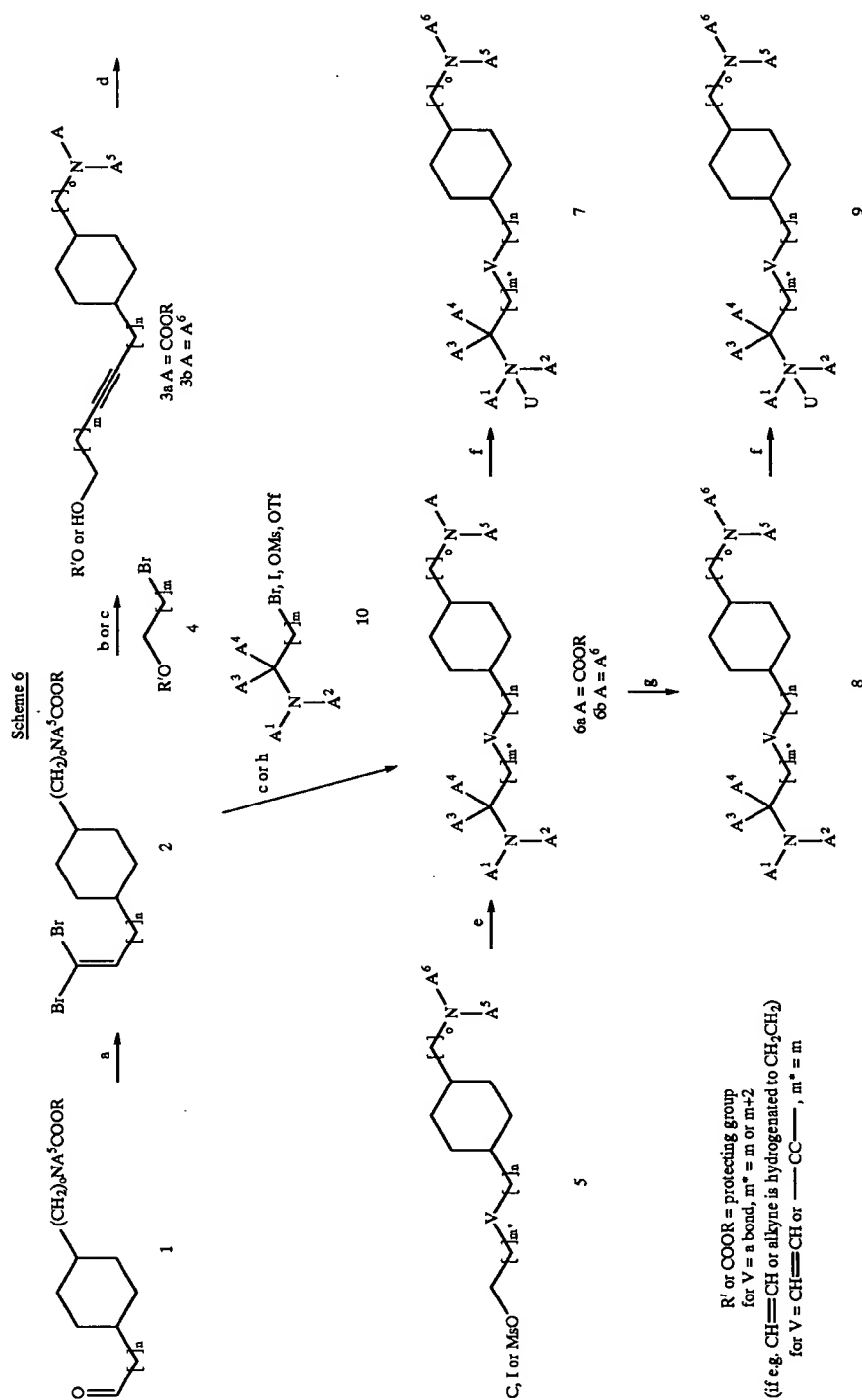
Scheme 3



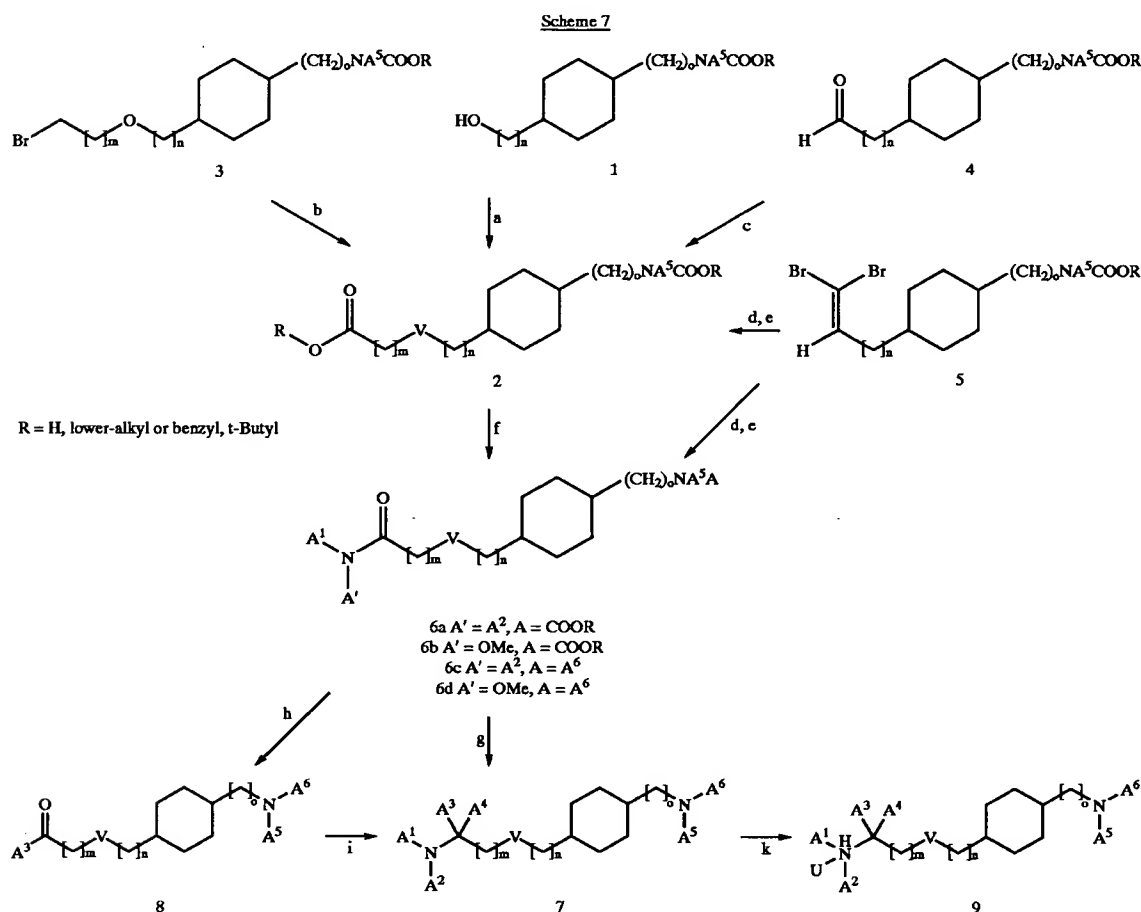


Scheme 5





R' or COOR = protecting group
for V = a bond, m* = m or m+2
(if e.g. $\text{CH}=\text{CH}$ or alkyne is hydrogenated to CH_2CH_2)
for V = $\text{CH}=\text{CH}$ or ---CC--- , m* = m

**[0164] Scheme 1:**

[0165] Scheme 1 to scheme 4 describe the synthesis of intermediates. Cis- or trans-(4-methylaminomethyl-cyclohexyl)-methanol (A⁵=Me) 2 can be obtained from cis- or trans-(4-hydroxymethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester 1 [U.S. (1998) U.S. Pat. No. 5,843,973 or U.S. (2000) U.S. Pat. No. 6,022,969 A] by treatment with lithium aluminium hydride in tetrahydrofuran between room temperature and the reflux temperature of the tetrahydrofuran (step a). Introduction of a tert-butoxycarbonyl protective function by treatment with di-tert-butyl-dicarbonate in methanol/triethylamine between -10° C. and room temperature gives compound 3 (A⁵=Me) (step b). Compound 1 can also be first O-protected and then N-alkylated at the tert-butoxycarbonyl protected amino function with an alkyl or alkenyl halide in the presence of a base like sodium hydride in a solvent like N,N-dimethylformamide or acetonitrile at temperatures between room temperature and 80° C. to introduce substituents A⁵; after O-deprotection the compound 3 is obtained. Compound 3 is subsequently oxidized to the corresponding aldehyde 4 by using e.g. Swern conditions: oxalyl chloride/dimethylsulfoxide/triethylamine in dichloromethane, -78° C. to room temperature (step c).

[0166] Scheme 2:

[0167] Cis or trans-[4-(Tert-butyl-dimethyl-silyloxymethyl)-cyclohexyl]-methanol 1 is prepared from the corresponding bis-hydroxymethyl cyclohexane derivatives by treatment with one equivalent of n-butyl lithium in tetrahydrofuran at -78° C. followed by one equivalent of tert-butyl-dimethyl-chlorosilane at -65° C. to room temperature. Mesylation of [4-(tert-butyl-dimethyl-silyloxymethyl)-cyclohexyl]-methanol 1 (methanesulfonyl chloride in dichloromethane and triethylamine at 0-10° C.) gives the corresponding methanesulfonate, which is treated with sodium cyanide in N,N-dimethylformamide at 80° C. to give the cyano compound 2 (step a). Direct reduction of the cyano compound 2 e.g. by hydrogenation with a platinum catalyst in acidic methanol gives the primary O-deprotected amine 3 (step b). Treatment of the amino-alcohol 3 first with di-tert-butyl-dicarbonate in dichloromethane in the presence of triethylamine followed by acetic anhydride and pyridine in dichloromethane gives the di-protected compound 4 (step c). Compound 4 can be N-alkylated at the primary tert-butoxycarbonyl protected amino function with an alkyl halide in the presence of a base like sodium hydride in a solvent like N,N-dimethylformamide or acetonitrile at tem-

peratures between room temperature and 80° C. to introduce substituents A⁵ and give, after basic cleavage of the acetate function, the primary hydroxy compound 5 (step d). The primary hydroxy compound 5 can be oxidized subsequently to the corresponding aldehyde 6 by using e.g. Swern conditions: oxalyl chloride/dimethylsulfoxide/triethylamine in dichloromethane, -78° C. to room temperature (step e).

[0168] Scheme 3:

[0169] Scheme 3 describes the synthesis of pure trans-aldehyde building block 8. Optionally A⁵ substituted cyclohexanol 1 is synthesized by hydrogenation of the corresponding 4-aminophenol, 4-hydroxybenzylamine or tyramine. Amine 1 is converted to the N-protected-derivative 2 (e.g. ZCl, Na₂CO₃/THF/H₂O) (step a). Oxidation with TEMPO (2,2,6,6-Tetramethylpiperidine 1-oxyl, radical) and sodium hypochlorite gives ketone 3 (step b). Wittig reaction with (methoxymethyl)triphenylphosphonium chloride 4 in THF and potassium t-butoxide as base gives enoether 5 (step c). A⁵-introduction is possible on this stage (with A⁵-halogenide/NaH in DMF or DMA). Hydrolyses of enoether 5 with 1 N HCl in THF at reflux (step d) gives aldehyde 6. The crude aldehyde 6 (as a cis/trans mixture) can be isomerised via bisulfite-adduct 7 (with disodium pyrosulfite in water/TBME, step e). Bisulfite adduct 7 can then be converted to the pure trans-aldehyde 8 with aqueous Na₂CO₃ in water/TBME (step f).

[0170] Scheme 4:

[0171] The preparation of the starting materials for cyclohexyl derivatives of formula (I) in which V is a single bond, O, S, —CH=CH—CH₂—O—, —CH=CH—, or —C=C—, is depicted in scheme 4. For compounds with n=0, the synthesis starts from cyclohexanol 1 which is converted to the Z-derivative or the BOC derivative 2 e.g. ZCl, Na₂CO₃, THF, H₂O or -(BOC)₂O, iPrOH, CH₂Cl₂, respectively (step a). Optionally A⁵ can be introduced in two ways. Lithium aluminum hydride reduction yields methylamino derivative which is e.g. BOC-protected to yield compounds 3. Compound 2 can also be first O-protected and then N-alkylated at the tert-butoxycarbonyl protected amino function with an A⁵-halide in the presence of a base like sodium hydride in a solvent like N,N-dimethylformamide or acetonitrile at temperatures between room temperature and 80° C. to introduce substituents A⁵; after O-deprotection compound 3 is obtained (step b) and then transferred into the desired A⁶-derivative 4b (step c).

[0172] Reaction of Step c may be Performed in Two Steps:

[0173] First step: If necessary, introduction of the HOCH₂(CH₂)_mV-Spacer (V=O or CH=CHCH₂O) with phase transfer conditions (e.g. α,ω-dihaloalkanes or α,ω-dihaloalkenes, NaOH, nBu₄NHSO₄) yields the corresponding halogenide, which is hydrolyzed to the alcohol (e.g. with aqueous NaOH in THF or DMA). Alternatively the Rⁿ protected RⁿOCH₂(CH₂)_mV-Spacer can be introduced with in situ generation of the RⁿOCH₂(CH₂)_mO-triflate (from the corresponding RⁿO-alkanol with trifluoromethanesulfonic anhydride/2,6-di-tert-butylpyridine in CH₂Cl₂ at 0° C.). This triflate is then reacted with alcohol 3 with 2,6-di-tert-butylpyridine as base in nitromethane at RT to 60° C. to yield RⁿOCH₂(CH₂)_mV-elongated 3 [following a procedure of Belostotskii, Anatoly M.; Hassner, Alfred. Synthetic methods. 41. Etherification of hydroxysteroids via triflates.

Tetrahedron Lett. (1994), 35(28), 5075-6]. These RⁿOCH₂(CH₂)_mV-elongated 3 are completely O- and N-deprotected (e.g. for Rⁿ=Bzl, with Pd/C and H₂ in EtOH or MeOH/AcOH and for NA⁵COOtBu with TFA in CH₂Cl₂ to give 4a).

[0174] Second step: Heteroaryl A⁶-introduction to give 4b can be done with different conditions: Method A: Reaction of compound 4a with 2-Halo-heteroaryl/N-ethyl-diisopropylamine 1b to 5 days at 80 to 120° C. in DMA or no solvent, or Method B (for less reactive compounds): Reaction of compound 4a with 2-Halo-heteroaryl/N-ethyl-diisopropylamine/CuI or NaI for 1-10 h at 120° C. or with microwave heating for 0.5 to 6 h at 120-150° C. in DMA.

[0175] For n=0, the starting material is cyclohexane-carboxylic acid 5 which is commercially available or can be synthesized (e.g. from aldehyde 6 by oxidation, scheme 3). Acid 5 is converted to the derivative 6 by ester formation (e.g. carbonyl-di-imidazole, methanol in THF) and optionally A⁵-alkylated using sodium hydride and a reactive alkyl or alkenyl derivative (step d). Reduction with lithium aluminum hydride yields the N-protected alcohol 7 which can be transformed to 4b (step f) as described for 3 to 4b.

[0176] For n=1, the starting material is cyclohexyl acetic acid 5 (can be derived from 4-nitrophenylacetic acid according to Karpavichyus, K. I.; Palaima, A. I.; Knunyants, I. L.; BACCAT; Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Transl.); EN; 29; 1980; 1689-1694; IASKA6; Izv. Akad. Nauk SSSR Ser. Khim.; RU; 10; 1980; 2374-2379 or T. P. Johnston et al. Journal of Medicinal Chemistry, 1977, Vol. No.2, 279-290.) which can be converted to the corresponding alcohol following the protocol for the compounds 5 to 4b. Alternatively cyclohexyl acetic acid 5 can be synthesized (e.g. from ketone 3 scheme 3; via C₂-elongation by Horner-Emmons reaction with triethyl phosphono acetate, sodium alcoholate) and protected as discussed before.

[0177] For n=2, the starting material is cyclohexane-carboxylic acid 5. Acid chain elongation (n>1) can be achieved using methods known in the art or as described below:

[0178] For C₂-elongation: Swern oxidation of the alcohol 7 to the corresponding aldehyde followed by Horner-Emmons reaction with triethyl phosphono acetate, sodium alcoholate in an alcohol gives the unsaturated ester 8 (step g). This can be subjected to hydrogenation with 10% palladium on carbon in methanol and reduction with lithium aluminum hydride in THF to yield the chain-elongated alcohol which can be transformed to 4b (step h) as described for 3 to 4b. The sequence 7->8 can be repeated to get the further C₂-elongated compounds 1f desired.

[0179] For C_(m)-elongation, Corey-Fuchs methodology may be used: Therefore, acid 5 is converted to the Weinreb derivative by treatment with N,O-dimethyl-hydroxylamine-hydrochloride with EDCI and HOBT in CH₂Cl₂ at room temperature, A⁵ alkylated (A⁵-halogenide with NaH in DMF or DMA at 0° C. to RT) and reduced by lithium aluminum hydride to the corresponding aldehyde 9 (step i). This aldehyde 9 can be treated with triphenylphosphine, tetrabromomethane and triethylamine in CH₂Cl₂ at 0° C. to RT to yield 2,2-Dibromo-vinyl derivative 10. Rearrangement with n-BuLi (ca 1.6 M in hexane) in THF at -78° C., followed by reaction with formaldehyde (-78° C. to RT)

gives the propargyl alcohol 12 [step 1, following conditions described in: Marshall, James A.; Bartley, Gary S.; Wallace, Eli M. Total Synthesis of the Pseudopterane (-)-Kallolide B, the Enantiomer of Natural (+)-Kallolide B. *J. Org. Chem.* (1996), 61(17), 5729-5735; and Baker, Raymond; Boyes, Alastair L.; Swain, Christopher J. Synthesis of talaromycins A, B, C, and E. *J. Chem. Soc., Perkin Trans. 1* (1990), (5), 1415-21.]. For longer side chains, the rearrangement is performed with *n*-BuLi (ca 1.6 M in hexane) in THF at -78° C. as described above, followed by addition of a cosolvent such as DMPU and reaction with O-protected 1-bromo-alcohols 11 (step m) to give the O-protected compounds 12.

[0180] O-deprotection (if necessary) and N-deprotection of 12 followed by reaction with the 2-Halo-heteroaryl, as described before (step n), yields derivatives 4b (V=—C≡C—). For V=—CH=CH— or single bond, hydrogenation of 12 e.g. with Raney-Ni, 10% Pd/C or PtO₂·H₂O/H₂ (step o) and reaction of compound 13 with the 2-Halo-heteroaryl, as described before (step n), yields derivatives 4b.

[0181] Finally, the substitution pattern for A⁶ in product 4b can be manipulated: e.g. by Suzuki reactions if A⁶ is a Halo-heteroaryl or by nucleophilic displacements, e.g. if A⁶ is 6-Chloro-pyridazine, reaction with sodium alcoholate in DMA at 80° C. gives the alkoxy substituted compound.

[0182] Scheme 5:

[0183] The synthesis of ether (V=O and S) derivatives of formula (I) is depicted in scheme 5. For the preparation of derivatives with n=0, the cyclohexanol derivative 1 (synthesis see scheme 1-4) can be treated under phase transfer conditions e.g. α,ω-dihaloalkanes or α,ω-dihaloalkenes, NaOH, *n*Bu₄NHSO₄ to yield bromide 2. For n>0, alcohol derivative 1 may be treated with α,ω-dihaloalkane (for C₄ or longer alkanes) in the presence of NaH in DMF 0° C. to RT to yield bromide 2. For shorter alkanes the method of choice is the in situ generation of the haloalkane-triflate (from the corresponding haloalkanol with trifluoromethanesulfonic anhydride/2,6-di-*tert*-butylpyridine in CH₂Cl₂ at 0° C.). This haloalkane-triflate is then reacted with alcohol 1 with 2,6-di-*tert*-butylpyridine as base in nitromethane at RT to 60° C. to yield bromide 2 [following a procedure of Belostotskii, Anatoly M.; Hassner, Alfred. *Synthetic methods*. 41. Etherification of hydroxysteroids via triflates. *Tetrahedron Lett.* (1994), 35(28), 5075-6].

[0184] Amination of bromide 2 with amine A¹A²NH in DMA or DMF, at RT or in MeOH at RT to reflux yields the final amine 3, optionally DBU may be added and NaI. In case A¹ or A² is a H, the second substituent can be introduced in a second step, e.g. N-methylation with NaH₂PO₃/formaldehyde. Amine 3 may be converted to a salt or to the N-oxide 4 using a mixture of hydrogen peroxide urea adduct and phthalic anhydride in CH₂Cl₂ at RT.

[0185] Alternatively, the alcohol 1 can be converted to the amine 5 by attaching the pre-assembled fragment A¹A²NC(A³A⁴)(CH₂)_m-VH (V=O and S), which can be synthesized by known methods, to the mesylate/halogenate of derivative 1 using alkylating conditions (step d). Alternatively, fragment A¹A²NC(A³A⁴)(CH₂)_m-OH can also be mesylated/halogenated and reacted with derivative 1 using alkylating conditions (step d). The amine 5 can be converted to its salt or the N-oxide 6 as described above (step c).

[0186] Finally, the substitution pattern for A⁶ in product 5 can be manipulated: e.g. hydrolysis of a N-acetyl group to an NH₂ or by Suzuki reactions if A⁶ is a Halo-heteroaryl or by nucleophilic displacements, e.g. if A⁶ is 6-Chloro-pyridazine, reaction with sodium alcoholate in DMA at 80° C. gives the alkoxy substituted compound.

[0187] Furthermore the substitution pattern of A¹ or A² may be modified, e.g. treatment of hydroxyethylamine with DAST.

[0188] Scheme 6:

[0189] In scheme 6 the synthesis of C-analogues cyclohexanes of the general structure I in which V is a single bond, —CH=CH— or —C≡C— is described. The synthesis starts from aldehyde 1 which is described in scheme 1-4. Side chain extension is effected through application of the Corey-Fuchs method. The aldehyde 1 is treated with triphenylphosphine, tetra-bromo-methane and triethylamine in CH₂Cl₂ at 0° C. to RT to yield 2,2-Dibromo-vinyl derivative 2. Rearrangement with *n*-BuLi (ca 1.6 M in hexane) in THF at -78° C., followed by reaction with formaldehyde (-78° C. to RT; step b) leads to the propargyl alcohol 3a [following conditions described in: Marshall, James A.; Bartley, Gary S.; Wallace, Eli M. Total Synthesis of the Pseudopterane (-)-Kallolide B, the Enantiomer of Natural (+)-Kallolide B. *J. Org. Chem.* (1996), 61(17), 5729-5735; and Baker, Raymond; Boyes, Alastair L.; Swain, Christopher J. Synthesis of talaromycins A, B, C, and E. *J. Chem. Soc., Perkin Trans. 1* (1990), (5), 1415-21.]. BOC-deprotection (TFA, CH₂Cl₂) followed by treatment with A⁶-heteroaryl as described before (scheme 4) gives compounds of the formula 3b.

[0190] For longer side chains, the rearrangement of dibromoalkene 2 is performed with *n*-BuLi (ca 1.6 M in hexane) in THF at -78° C. as above, followed by addition of a cosolvent such as DMPU and reaction with O-protected 1-bromo-alcohols 4 to yield the O-protected compounds 3a which can be deprotected to the corresponding alkyne 3a derivative in MeOH at 50-60° C. in the presence of catalytic amount of pyridinium toluene-4-sulfonate. BOC-deprotection (TFA, CH₂Cl₂) followed by treatment with A⁶-heteroaryl as described before (scheme 4) gives compounds of the formula 3b (step c).

[0191] Mesylation of alcohol 3b with methanesulfonylchloride, pyridine or lutidine with or without DMAP in CH₂Cl₂ at 0° C. to RT yields mesylate/chloride or pyridinium derivative 5 which can be converted to the amine 6b in DMA or MeOH at RT or at 50-70° C. with an excess of the corresponding amine NHA¹A² (step e). In case A¹ or A² is a H, the second substituent can be introduced in a second step, e.g. N-methylation with NaH₂PO₃/formaldehyde.

[0192] To obtain compounds 6b in which A³ and/or A⁴ is not H and m>0, compounds 2 can be reacted with compounds 10 under the same condition as described for step c. The building blocks 10 can be prepared by known methods.

[0193] For the introduction of the group (A¹A²)N—C(A³, A⁴)- wherein A³ and/or A⁴ is not H and m=0, a two step procedure has to be followed: first the rearrangement dibromide 2 with *n*-BuLi (ca 1.6 M in hexane) in THF at -78° C., followed by reaction with the corresponding aldehyde (A³ or A⁴-COH) or ketone (A³COA⁴, at -78° C. to RT) leading to the A³A⁴ substituted propargyl alcohol which can be transformed to a phosphorester [see: Bartlett, Paul A.; McQuaid,

Loretta A. Total synthesis of (\pm)-methyl shikimate and (\pm)-3-phosphoshikimic acid. *J. Am. Chem. Soc.* (1984), 106(25), 7854-60] and reacted with the desired (A^1, A^2)-amine in the presence of Tetrakis(triphenylphosphine)-palladium in THF to yield the desired A^3, A^4 -substituted compound 6a (step h). BOC-deprotection (TFA, CH_2Cl_2) followed by treatment with A^6 -heteroaryl as described before (scheme 4) gives compounds of the formula 6b.

[0194] Compounds in which V is a single bond or $-CH=CH-$ can be obtained by hydrogenation of compound 6b with $PtO_2 \cdot H_2O/H_2$ (yields the saturated analogue 8) or by hydrogenation with other known methods (e.g. Raney-Ni, yields the double bond analogue 8). Alternatively, the alkyne group can already be reduced at an earlier stage e.g. alcohol 3a (e.g. LAH-reduction for $m=0$, gives $V=trans-CH=CH-$ or hydrogenation with Pt/C or $PtO_2 \cdot H_2O$ yields $V=CH_2CH_2-$ (single bond respectively)), and the resulting compound can then be transformed further to the final compounds 8 and/or 9.

[0195] Finally, the substitution pattern for A^6 in product 6b or 8 can be manipulated: e.g. hydrolysis of a N-acetyl group to an NH_2 or by Suzuki reactions if A^6 is a Halo-heteroaryl or by nucleophilic displacements, e.g. if A^6 is 6-Chloro-pyridazine, reaction with sodium alcoholate in DMA at 80° C. gives the alkoxy substituted compound.

[0196] Furthermore the substitution pattern of A^1 or A^2 may be modified, e.g. treatment of hydroxyethylamine with DAST. In case A^1 or A^2 is a H, the second substituent can be introduced in a second step, e.g. N-methylation with NaH_2PO_3 /formaldehyde.

[0197] The amines 6b and 8 can be converted to a salt or as described in step f to the N-oxide 7 and 9, respectively, using a mixture of hydrogen peroxide urea adduct and phthalic anhydride in CH_2Cl_2 at RT.

[0198] Scheme 7:

[0199] Another possible approach for the introduction of the substituted side chain is depicted in scheme 7. The synthesis of the main intermediate 2 begins by attaching an ω -hydroxyalkylcarboxylic acid ester to alcohol 1 via the in situ generated triflate in analogy to Belostotskii, Anatoly M.; Hassner, Alfred. *Synthetic methods*. 41. Etherification of hydroxysteroids via triflates. *Tetrahedron Lett.* (1994), 35(28), 5075-6 (step a). Alternatively, the ester 2 can be prepared from the bromide 3 (synthesis described in scheme 5) by treatment with e.g. acetocyanhydrine in acetonitrile, followed by a Pinner reaction and hydrolysis of the imidate to the corresponding ester (step b).

[0200] For $V=CH=CH$, the ester 2 or its corresponding acid may be prepared from aldehyde 4 (synthesis described in scheme 1-4) by treatment with the corresponding Wittig reagent $Ph_3P(CH_2)_{m+1}CO_2R/H$. For $V=a$ bond, hydrogenation of the Wittig product under standard conditions yields the saturated product 2.

[0201] For $V=C=C$, ester 2 or amide 6a may be derived from the dibromoderivative 5 (synthesis according to scheme 4) by rearrangement with $n-BuLi$ (ca 1.6 M in hexane) in THF at $-78^\circ C$, followed by reaction with chloroformate ($\rightarrow 2$) or dialkylcarbamoyl chloride ($\rightarrow 6a$) ($-78^\circ C$ to RT; step d). For longer side chains, the rearrangement of dibromoalkene 5 may be performed with

$n-BuLi$ (ca 1.6 M in hexane) in THF at $-78^\circ C$. as above, followed by addition of a cosolvent such as DMPU and reaction with a suitable protected 1-bromo-alkylalcohol $Br-(CH_2)_mCH_2OH$, followed by oxidation to yield the compound 2 as acid (step e).

[0202] Saponification of the ester 2 using standard conditions e.g. $LiOH$ in $EtOH$, $MeOH$ or THF , followed by treatment with NHA^1A^2 or NHA^1A' , $EDCl$, $HOBT$ and a base such as Huenig's base, NEt_3 , NMM in CH_2Cl_2 , DMF , DMA or dioxane gives amide 6a or 6b. N-deprotection of 6a or 6b followed by reaction with the 2-Halo-heteroaryl, as described in scheme 4 yields derivatives 6c and 6d.

[0203] Amide 6c can be transferred to amine 7 ($A^3, A^4=Me$) by reaction with methylmagnesium bromide, $ZrCl_4$ in THF at low temperature (see Stephen M. Denton, Anthony Wood, A Modified Bouveault Reaction for the Preparation of α, α -dimethylamines from Amides, *Synlett* 1999, 1, 55-56.) or by treatment with other grignard reagents in the presence of $ZrCl_4$ or $Ti(OiPr)_4$ (see V. Chalinski, A. de Meijere, A versatile New Preparation of Cyclopropylamines from acid dialkylamides, *Angew. Chem. Int. Ed. Engl.* 1996, 35, No.4, 413-4.).

[0204] For $A^1=Me$, $A'=OMe$, amide 6d can be treated with a grignard reagent A^3MgX to give the corresponding ketone 8. Reductive alkylation of the ketone 8 by treatment with NHA^1A^2 in the presence of tetraisopropyl orthotitanate, followed by reduction with $NaCNBH_3$ in ethanol yields the amine 7 (see: R. J. Mattson, K. M. Pham, D. J. Leuck, K. A. Cowen, J. O. C. 1990, 55, 2552-4.).

[0205] Finally, the substitution pattern for A^6 in product 7 can be manipulated: e.g. hydrolysis of a N-acetyl group to an NH_2 or by Suzuki reactions if A^6 is a Halo-heteroaryl or by nucleophilic displacements, e.g. if A^6 is 6-Chloro-pyridazine, reaction with sodium alcoholate in DMA at 80° C. gives the alkoxy substituted compound.

[0206] Furthermore the substitution pattern of A^1 or A^2 may be modified, e.g. treatment of hydroxyethylamine with DAST. In case A^1 or A^2 is a H, the second substituent can be introduced in a second step, e.g. N-methylation with NaH_2PO_3 /formaldehyde.

[0207] Amine 7 may be converted to a salt or to the N-oxide 9 using a mixture of hydrogen peroxide urea adduct and phthalic anhydride in CH_2Cl_2 at RT.

[0208] Pure cis- or trans-aminocyclohexane derivatives can be obtained either by separation of the mixtures using HPLC or by using stereochemically defined starting materials.

[0209] The following tests were carried out in order to determine the activity of the compounds of formula I and their salts.

[0210] Inhibition of Human Liver Microsomal 2,3-oxidosqualene-lanosterol Cyclase (OSC)

[0211] Liver microsomes from a healthy volunteer were prepared in sodium phosphate buffer (pH 7.4). The OSC activity was measured in the same buffer, which also contained 1 mM EDTA and 1 mM dithiothreitol. The microsomes were diluted to 0.8 mg/ml protein in cold phosphate buffer. Dry [^{14}C]R,S-monooxidosqualene (MOS, 12.8 mCi/mmol) was diluted to 20 nCi/ μ l with ethanol and

mixed with phosphate buffer-1% BSA (bovine serum albumin). A stock solution of 1 mM test substance in DMSO was diluted to the desired concentration with phosphate buffer-1% BSA. 40 μ l of microsomes were mixed with 20 μ l of the solution of the test substance and the reaction was subsequently started with 20 μ l of the [14 C] R,S-MOS solution. The final conditions were: 0.4 mg/ml of microsomal proteins and 30 μ l of [14 C]R,S-MOS in phosphate buffer, pH 7.4, containing 0.5% albumin, DMSO <0.1% and ethanol <2%, in a total volume of 80 μ l.

[0212] After 1 hour at 37° C. the reaction was stopped by the addition of 0.6 ml of 10% KOH-methanol, 0.7 ml of water and 0.1 ml of hexane:ether (1:1, v/v) which contained 25 μ g of non-radioactive MOS and 25 μ g of lanosterol as carriers. After shaking, 1 ml of hexane:ether (1:1, v/v) was added to each test tube, these were again shaken and then centrifuged. The upper phase was transferred into a glass test tube, the lower phase was again extracted with hexane:ether and combined with the first extract. The entire extract was evaporated to dryness with nitrogen, the residue was suspended in 50 μ l of hexane:ether and applied to a silica gel plate. Chromatographic separation was effected in hexane:ether (1:1, v/v) as the eluent. The R_f values for the MOS substrate and the lanosterol product were 0.91 and, respectively, 0.54. After drying, radioactive MOS and lanosterol were observed on the silica gel plate. The ratio of MOS to lanosterol was determined from the radioactive bands in order to determine the yield of the reaction and OSC inhibition.

[0213] The test was carried out on the one hand with a constant test substance concentration of 100 nM and the percentage OSC inhibition against controls was calculated. The more preferred compounds of the present invention exhibit inhibitions larger than 50%. In addition, the test was carried out with different test substance concentrations and subsequently the IC₅₀ value was calculated, i.e. the concentration required to reduce the conversion of MOS into lanosterol to 50% of the control value. The preferred compounds of the present invention exhibit IC₅₀ values of 1 nM to 10 μ M, preferably of 1-100 nM.

[0214] The compounds of formula I and/or their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical preparations for enteral, parenteral or topical administration. They can be administered, for example, perorally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions or infusion solutions, or topically, e.g. in the form of ointments, creams or oils. Oral administration is preferred.

[0215] The production of the pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula I and/or their pharmaceutically acceptable salts, optionally in combination with other therapeutically valuable substances, into a galenic administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

[0216] Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for

example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers might, however, be required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar and the like. Suitable carrier materials for injection solutions are, for example, water, alcohols, polyols, glycerol and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

[0217] Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavour-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

[0218] The dosage of the compounds of formula I can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage of about 1 to 1000 mg, especially about 1 to 100 mg, comes into consideration. Depending on severity of the disease and the precise pharmacokinetic profile the compound could be administered with one or several daily dosage units, e.g. in 1 to 3 dosage units.

[0219] The pharmaceutical preparations conveniently contain about 1-500 mg, preferably 1-100 mg, of a compound of formula I.

[0220] The following Examples serve to illustrate the present invention in more detail. They are, however, not intended to limit its scope in any manner.

EXAMPLES

[0221] Abbreviations:

[0222] AcOH=Acetic acid, BOC=t-Butyloxycarbonyl, BuLi=Butyllithium, CH₂Cl₂=dichloromethane, DAST=Diethylamino-sulphurtrifluoride, DEAD=Diethyl azodicarboxylate, DBU=1,8-Diazabicyclo[5.4.0]undec-7-ene(1,5-5), DIBALH=Di-1-butylaluminium hydride, DMA N,N-Dimethylacetamide, DMAP=4-Dimethylaminopyridine, DMF=N,N-Dimethylformamide, DMPU=1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone, EDCI=N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, EtOAc=Ethylacetate, EtOH=Ethanol, Et₂O=Diethylether, Et₃N=Triethylamine, eq=Equivalents, HOBT=1-Hydroxybenzo-triazole, Huenig's base=iPr₂NEt=N-Ethyl diisopropylamine, LAH=Lithium aluminium hydride, LDA=Lithium diisopropylamide, LiBH₄=Lithium borohydride, MeOH=Methanol, NaI=Sodium iodide, PdCl₂(dppf)=(1,1'-Bis(diphenylphosphino)ferrocene)dichloropalladium(II).CH₂Cl₂ (1:1), Pd(Ph₃P)₄=Tetrakis(triphenylphosphine)palladium, Red-Al=Sodium bis(2-

methoxyethoxy) aluminium hydride, TEMPO=2,2,6,6-Tetramethylpiperidine 1-oxyl, radical, TBDMSCl=t-Butyldimethylsilyl chloride, TBME=t-Butyl methyl ether, TFA=Trifluoroacetic acid, THF=Tetrahydrofuran, quant=quantitative.

[0223] General Remarks

[0224] All reactions were performed under argon.

Example 1

[0225] 1.1

[0226] A solution of 20 g (82.2 mmol) trans-4-tert-Butoxycarbonylamino-cyclohexanecarboxylic acid in 1.2 l CH_2Cl_2 was treated with 12.83 g (131.5 mmol) N,O-dimethyl-hydroxylamine hydrochloride, 10.85 ml (98.6 mmol) N-methylmorpholine and at 0° C. with 18.91 g (98.64 mmol) EDCI and 12.62 g (82.2 mmol) HOBt. The reaction mixture was stirred 2 h at room temperature and extracted with aqueous 10% $\text{KHSO}_4/\text{Et}_2\text{O}$ (3 \times). The organic phases were washed with aqueous saturated NaHCO_3 , 10% NaCl and dried over Na_2SO_4 to yield 24.25 g (quantitative) of trans-[4-(Methoxy-methyl-carbamoyl)-cyclohexyl]-carbamic acid tert-butyl ester, mp: 130-140° C., slowly dec.; MS: 287 (MH^+).

[0227] 1.2

[0228] A solution of 24.18 g (82 mmol) of trans-[4-(Methoxy-methyl-carbamoyl)-cyclohexyl]-carbamic acid tert-butyl ester in 80 ml of DMF was treated at 0° C. with 5.37 g (123 mmol) of NaH (55% in oil) in small portions. The reaction was stirred for 1 h at 0° C., then treated slowly (20 min) with 40.9 ml (656 mmol) iodomethane and warmed up to RT over night. The reaction was cooled and neutralized with aqueous 10% KHSO_4 and poured into water/ Et_2O (3 \times). The organic phase was washed with aqueous 10% NaCl, dried over Na_2SO_4 evaporated and purified by flash silica gel column ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 9:1 to 1:1) to yield 20.69 g (84%) of trans-[4-(Methoxy-methyl-carbamoyl)-cyclohexyl]-methyl-carbamic acid tert-butyl ester, MS: 301 (MH^+).

[0229] 1.3

[0230] A solution of 2.09 g (55 mmol) LAH in 250 ml THF was cooled (-50° C.) and treated during 25 min with a solution of 15.02 g (50 mmol) of trans-[4-(Methoxy-methyl-carbamoyl)-cyclohexyl]-methyl-carbamic acid tert-butyl ester in 250 ml THF. The reaction was warmed up to +15° C. for 3.5 h, cooled (-78° C.) and hydrolyzed with a suspension of 15 g $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$, 15 g silicagel in 50 ml aqueous 10% KHSO_4 . The cooling bath was removed, THF was added, the mixture was stirred for 30 min and filtered. After evaporation, the residue was dissolved in CH_2Cl_2 , dried over Na_2SO_4 and evaporated to yield 12.83 (quantitative) of trans-(4-Formyl-cyclohexyl)-methyl-carbamic acid tert-butyl ester, MS: 241 (M).

[0231] 1.4

[0232] A solution of 52.45 g (200 mmol) triphenylphosphine in 200 ml CH_2Cl_2 was treated with 33.16 g (100 mmol) tetrabromomethane (the reaction heated up to reflux) and after 50 min with 32.06 ml (230 mmol) triethylamine (the reaction heated up to reflux and became dark violet). After cooling (0° C.), 12.83 g (50 mmol) of trans-(4-Formyl-cyclohexyl)-methyl-carbamic acid tert-butyl ester in 125 ml

CH_2Cl_2 were added during 10 min. The solution was stirred for 16 h at RT, evaporated and filtered through silica gel (deactivated with hexane/0.5% Et_3N) with hexane and then hexane/ Et_2O 4:1 to 1:1 as eluent to yield 13.28 g (67%) of trans-[4-(2,2-Dibromo-vinyl)-cyclohexyl]-methyl-carbamic acid tert-butyl ester, mp: 93-99° C., dec.; MS: 396 (MH^+ , 2Br).

[0233] 1.5

[0234] The following reaction was performed in analogy to the reaction described in:

[0235] Marshall, James A.; Bartley, Gary S.; Wallace, Eli M. Total Synthesis of the Pseudopterane (-)-Kallolide B, the Enantiomer of Natural (+)-Kallolide B. J. Org.

[0236] Chem. (1996), 61(17), 5729-5735 and Baker, Raymond; Boyes, Alastair L.; Swain, Christopher J. Synthesis of talaromycins A, B, C, and E. J. Chem. Soc., Perkin Trans. 1 (1990), (5), 1415-21.). A solution of 993 mg (2.5 mmol) of trans-[4-(2,2-Dibromo-vinyl)-cyclohexyl]-methyl-carbamic acid tert-butyl ester in 20 ml THF was treated at -78° C. with 3.28 ml (5.25 mmol) of BuLi (ca 1.6 M in hexane). After 2 h at this temperature 790 mg (25 mmol) of paraformaldehyde were added. The reaction mixture was warmed up to RT for 3 h and after 1 h at this temperature extracted with water/ Et_2O (3 \times). The organic phases were washed with aqueous 10% NaCl, dried over Na_2SO_4 and evaporated. Purification by flash-chromatography on silica gel (hexane/ EtOAc 4:1) yielded 530 mg (79%) of trans-[4-(3-Hydroxy-prop-1-ynyl)-cyclohexyl]-methyl-carbamic acid tert-butyl ester, MS: 268 (MH^+).

[0237] 1.6

[0238] A solution of 9.0 g (33.66 mmol) of trans-[4-(3-Hydroxy-prop-1-ynyl)-cyclohexyl]-methyl-carbamic acid tert-butyl ester in 185 ml CH_2Cl_2 was treated at 0° C. with 136 ml of TFA (for 30 min). After 15 min at this temperature, the reaction was evaporated, treated with cold (0° C.) 1 N NaOH (saturated with NaCl) and extracted with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1 (3 \times). The organic phase was dried over Na_2SO_4 and evaporated to yield 5.84 g (quantitative) of trans-3-(4-Methylamino-cyclohexyl)-prop-2-yn-1-ol, MS: 167 (M).

[0239] 1.7

[0240] A mixture of 0.51 g (3.05 mmol) trans-3-(4-Methylamino-cyclohexyl)-prop-2-yn-1-ol, 0.87 g (3.66 mmol) 2,5-dibromo-pyrimidine [Brown, Desmond J.; Arantz, B. W., Pyrimidine reactions. XXII. Relative reactivities of corresponding chloro-, bromo-, and iodopyrimidines in aminolysis. J. Chem. Soc. C (1971), Issue 10, 1889-91] and 1.78 ml (10.34 mmol) N-ethyldiisopropylamine was heated for 2.5 h at 80° C. The reaction was cooled, evaporated and partitioned between aqueous saturated $\text{NaHCO}_3/\text{Et}_2\text{O}$ (3 \times). The organic phases were washed with aqueous 10% NaCl, dried (NaSO_4) and evaporated. Flash chromatography on silica gel (hexane/ EtOAc 95:5) gave 0.72 g (73%) of trans-3-[4-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-cyclohexyl]-prop-2-yn-1-ol, mp: 156-157° C.; MS: 324 (MH^+ , 1Br).

[0241] 1.8

[0242] In analogy to example 1.7, trans-3-(4-Methylamino-cyclohexyl)-prop-2-yn-1-ol and 3.2 equivalent of 2-chloro-pyrimidine gave after 3 h at 80° C. trans-3-[4-

(Methyl-pyrimidin-2-yl-amino)-cyclohexyl}-prop-2-yn-1-ol, mp: 138-140° C., dec.; MS: 245 (M).

[0243] 1.9

[0244] In analogy to example 1.7, trans-3-(4-Methylamino-cyclohexyl)-prop-2-yn-1-ol and 1.2 equivalent of 2-chloropyridine-5-carbonitrile gave after 29 h at 80° C. trans-6-[[4-(3-Hydroxy-prop-1-ynyl)-cyclohexyl]-methyl-amino]-nicotinonitrile, mp: 126.1-127.4; MS: 270 (MH⁺).

[0245] 1.10

[0246] In analogy to example 1.7, trans-3-(4-Methylamino-cyclohexyl)-prop-2-yn-1-ol and 1.5 equivalent of 2-Bromo-5-chloro-pyrimidine [synthesized from 5-chloro-2-hydroxy-pyrimidine in analogy to Brown, Desmond J.; Arantz, B. W., Pyrimidine reactions. XXII. Relative reactivities of corresponding chloro-, bromo-, and iodopyrimidines in aminolysis. J. Chem. Soc. C (1971), Issue 10, 1889-91] were heated for 0.5 h at 80° C., 1 h at 120° C., then 0.5 equivalent of 2-Bromo-5-chloro-pyrimidine were added and heated for 1 h at 120° C. to give after work up trans-3-[4-[(5-Chloro-pyrimidin-2-yl)-methyl-amino]-cyclohexyl]-prop-2-yn-1-ol, mp: 148-150° C., dec.; MS: 280 (MH⁺, 1Cl).

[0247] 1.11

[0248] A mixture of 0.67 g (4 mmol) trans-3-(4-Methylamino-cyclohexyl)-prop-2-yn-1-ol, 2.76 g (18 mmol) of 3,6-dichloropyridazine and 1.76 ml (13.6 mmol) N-ethyl-diisopropylamine was heated for 3.5 h at 80° C., diluted with 1 ml DMF and heated for 4 days at 80° C. and one day at 120° C. The reaction was cooled, evaporated and partitioned between aqueous saturated NaHCO₃/Et₂O (3x). The organic phases were washed with aqueous 10% NaCl, dried (Na₂SO₄) and evaporated. Flash chromatography on silica gel (MeCl₂/Et₂O 95:5 to 9:1) gave 0.61 g (54%) of trans-3-[4-[(6-Chloro-pyridazin-3-yl)-methyl-amino]-cyclohexyl]-prop-2-yn-1-ol, MS: 280 (MH⁺, 1Cl).

[0249] 1.12

[0250] A mixture of 0.67 g (4 mmol) trans-3-(4-Methylamino-cyclohexyl)-prop-2-yn-1-ol,

[0251] 1.24 ml (12 mmol) of 5-bromo-2-fluoropyridine and 1.76 ml (13.6 mmol) N-ethyl-diisopropylamine was heated for 3 h at 80° C. and 24 h at 120° C. The mixture was diluted with 1 ml DMF, treated with a catalytic amount of NaI and heated for 2 days at 120° C. The reaction was cooled, evaporated and partitioned between aqueous saturated NaHCO₃/Et₂O (3x). The organic phases were washed with aqueous 10% NaCl, dried (Na₂SO₄) and evaporated. Flash chromatography on silica gel (MeCl₂/Et₂O 97.5:2.5 to 92.5:7.5) gave 0.57 g (44%) of trans-3-[4-[(5-Bromo-pyridin-2-yl)-methyl-amino]-cyclohexyl]-prop-2-yn-1-ol, MS: 323 (MH⁺, 1Br).

[0252] 1.13

[0253] In analogy to example 1.12, trans-3-(4-Methylamino-cyclohexyl)-prop-2-yn-1-ol and 2-fluoropyridine gave after 5 days at 120° C. trans-3-[4-(Methyl-pyridin-2-yl-amino)-cyclohexyl]-prop-2-yn-1-ol, MS: 245 (MH⁺).

[0254] 1.14

[0255] In analogy to example 1.12, trans-3-(4-Methylamino-cyclohexyl)-prop-2-yn-1-ol and 2-chloropyrazine gave trans-3-[4-(Methyl-pyrazin-2-yl-amino)-cyclohexyl]-prop-2-yn-1-ol, mp: 147-149° C., dec.; MS: 246 (MH⁺).

[0256] 1.15

[0257] A solution of 0.24 g (1.44 mmol) of trans-3-(4-Methylamino-cyclohexyl)-prop-2-yn-1-ol, 0.7 ml (5.74 mmol) of 2-chloro-5-ethylpyrimidine, 0.83 ml (4.88 mmol) N-ethyl-diisopropylamine and a catalytic amount of NaI in 1.5 ml DMA was heated in the microwave oven for 3.75 h at 120° C. The reaction was cooled and partitioned between aqueous saturated NaHCO₃/Et₂O (3x). The organic phases were washed with aqueous 10% NaCl, dried (Na₂SO₄) and evaporated. Flash chromatography on silica gel (hexane/EtOAc 9:1 to 1:1) gave 0.24 g (61%) of trans-3-[4-[(5-Ethyl-pyrimidin-2-yl)-methyl-amino]-cyclohexyl]-prop-2-yn-1-ol, MS: 274 (MH⁺).

[0258] 1.16

[0259] In analogy to example 1.15, trans-3-(4-Methylamino-cyclohexyl)-prop-2-yn-1-ol and 3-chloro-6-methylpyridazine gave, with no NaI after 4 h at 150° C. and 3/4 h at 120° C. in the microwave oven, trans-3-[4-[Methyl-(6-methyl-pyridazin-3-yl)-amino]-cyclohexyl]-prop-2-yn-1-ol, MS: 260 (MH⁺).

[0260] 1.17

[0261] A solution of 420 mg (1.3 mmol) of trans-3-[4-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-cyclohexyl]-prop-2-yn-1-ol in 10 ml CH₂Cl₂ was treated at 0° C. with 0.11 ml (1.43 mmol) methanesulfonylchloride, 0.16 ml (1.95 mmol) pyridine and 159 mg (1.3 mmol) DMAP. The reaction was stirred for 3.5 h at room temperature, water (2 ml) was added and stirred for 5 min. After extraction with aqueous saturated NaHCO₃/Et₂O (3x), the organic phase was washed with aqueous 10% NaCl, dried over Na₂SO₄ and evaporated to yield 540 mg (quantitative) of trans-Methanesulfonic acid 3-[4-[(5-bromo-pyrimidin-2-yl)-methyl-amino]-cyclohexyl]-prop-2-ynyl ester, MS: 402 (MH⁺, 1Br).

[0262] 1.18

[0263] In analogy to example 1.17, trans-3-[4-(Methyl-pyrimidin-2-yl-amino)-cyclohexyl]-prop-2-yn-1-ol was converted to trans-Methanesulfonic acid 3-[4-(methyl-pyrimidin-2-yl-amino)-cyclohexyl]-prop-2-ynyl ester, MS: 402 (MH⁺).

[0264] 1.19

[0265] In analogy to example 1.17, trans-6-[[4-(3-Hydroxy-prop-1-ynyl)-cyclohexyl]-methyl-amino]-nicotinonitrile was converted to trans-Methanesulfonic acid 3-[4-[(5-cyano-pyridin-2-yl)-methyl-amino]-cyclohexyl]-prop-2-ynyl ester, MS: 348 (MH⁺).

[0266] 1.20

[0267] In analogy to example 1.17, trans-3-[4-[(5-Chloro-pyrimidin-2-yl)-methyl-amino]-cyclohexyl]-prop-2-yn-1-ol was converted to trans-Methanesulfonic acid 3-[4-[(5-chloro-pyrimidin-2-yl)-methyl-amino]-cyclohexyl]-prop-2-ynyl ester, MS: 357 (MH⁺, 1Cl).

[0268] 1.21

[0269] In analogy to example 1.17, trans-3-{4-[(6-Chloro-pyridazin-3-yl)-methyl-amino]-cyclohexyl}-prop-2-yn-1-ol was converted to trans-Methanesulfonic acid 3-{4-[(6-chloro-pyridazin-3-yl)-methyl-amino]-cyclohexyl}-prop-2-ynyl ester, MS: 358 (MH⁺, 1Cl).

[0270] 1.22

[0271] In analogy to example 1.17, trans-3-{4-[(5-Bromo-pyridin-2-yl)-methyl-amino]-cyclohexyl}-prop-2-yn-1-ol was converted to trans-Methanesulfonic acid 3-{4-[(5-bromo-pyridin-2-yl)-methyl-amino]-cyclohexyl}-prop-2-ynyl ester, MS: 401 (MH⁺, 1Br).

[0272] 1.23

[0273] In analogy to example 1.17, trans-3-{4-(Methyl-pyridin-2-yl-amino)-cyclohexyl}-prop-2-yn-1-ol was converted to trans-Methanesulfonic acid 3-{4-(methyl-pyridin-2-yl-amino)-cyclohexyl}-prop-2-ynyl ester, MS: 323 (MH⁺).

[0274] 1.24

[0275] In analogy to example 1.17, trans-3-{4-(Methyl-pyrazin-2-yl-amino)-cyclohexyl}-prop-2-yn-1-ol was converted to trans-Methanesulfonic acid 3-{4-(methyl-pyrazin-2-yl-amino)-cyclohexyl}-prop-2-ynyl ester, MS: 324 (MH⁺).

[0276] 1.25

[0277] In analogy to example 1.17, trans-3-{4-[(5-Ethyl-pyrimidin-2-yl)-methyl-amino]-cyclohexyl}-prop-2-yn-1-ol was converted to trans-1-(3-{4-[(5-Ethyl-pyrimidin-2-yl)-methyl-amino]-cyclohexyl}-prop-2-ynyl)-pyridinium; methanesulfonate, MS: 335 (MH⁺).

[0278] 1.26

[0279] A solution of 0.246 g (0.95 mmol) of trans-3-{4-[Methyl-(6-methyl-pyridazin-3-yl)-amino]-cyclohexyl}-prop-2-yn-1-ol in 7 ml CH₂Cl₂ was treated at 0° C. with 0.081 ml (1.04 mmol) methanesulfonylchloride and 0.17 ml (1.42 mmol) 2,6-lutidine. The reaction was stirred for 22 h at room temperature, water (1 ml) was added and stirred for 5 min. After extraction with aqueous saturated NaHCO₃/Et₂O(3x), the organic phase was washed with aqueous 10% NaCl, dried over Na₂SO₄ and evaporated to yield 0.285 g of crude trans-[4-(3-Chloro-prop-1-ynyl)-cyclohexyl]-methyl-(6-methyl-pyridazin-3-yl)-amine, MS: 278 (MH⁺, 1Cl).

Example 2

[0280] A solution of 125 mg (corresponding to 0.30 mmol) of crude trans-Methanesulfonic acid 3-{4-[(5-bromo-pyrimidin-2-yl)-methyl-amino]-cyclohexyl}-prop-2-ynyl ester in 3 ml of methanol was cooled (0° C.), treated with 0.54 ml (3 mmol) of Dimethylamine (33% in EtOH 5.6M) and stirred for 20 h at RT. The solvent was evaporated and the residue extracted with aqueous saturated NaHCO₃/Et₂O (3x). The organic phase was dried with Na₂SO₄, filtered and evaporated. Purification by flash column chromatography on silica gel (CH₂Cl₂/MeOH 99:1 to 97.5:2.5) gave 65 mg (62%) of pure trans-(5-Bromo-pyrimidin-2-yl)-[4-(3-dimethylamino-prop-1-ynyl)-cyclohexyl]-methyl-amine, mp: 83-84° C., dec.; MS: 351 (MH⁺, 1Br).

[0281] The following compounds were prepared from the corresponding mesylates, chlorides or pyridinium-derivatives and secondary amines (In case the reaction was not finished after 20 h, additional amine (5 eq) was added and in cases denoted with * also a catalytic amount of NaI, the reaction was stirred for further 24 h.):

Example	Compound	MS MH ⁺	Mp ° C.	Mesylate/Chloride/ pyridinium-derivatives	Secondary amine
2.1	trans-{4-[3-(Allyl-methyl-amino)-prop-1-ynyl]-cyclohexyl}-(5-bromo-pyrimidin-2-yl)-methyl-amine	377, 1Br		trans-Methanesulfonic acid 3-{4-[(5-bromo-pyrimidin-2-yl)-methyl-amino]-cyclohexyl}-prop-2-ynyl ester	N-Allylmethyl-amine
2.2	trans-(5-Bromo-pyrimidin-2-yl)-methyl-{4-[3-(methyl-propyl-amino)-prop-1-ynyl]-cyclohexyl}-amine	379, 1Br		trans-Methanesulfonic acid 3-{4-[(5-bromo-pyrimidin-2-yl)-methyl-amino]-cyclohexyl}-prop-2-ynyl ester	N-Methylpropyl-amine
2.3	trans-(5-Bromo-pyrimidin-2-yl)-(4-{3-[ethyl-(2-methoxy-ethyl)-amino]-prop-1-ynyl}-cyclohexyl)-methyl-amine	409, 1Br		trans-Methanesulfonic acid 3-{4-[(5-bromo-pyrimidin-2-yl)-methyl-amino]-cyclohexyl}-prop-2-ynyl ester	N-(2-Methoxyethyl)-ethyl-amine
2.4	trans-{2-[3-{4-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-cyclohexyl}-prop-2-ynyl]-ethyl-amino]-ethanol}	395, 1Br		trans-Methanesulfonic acid 3-{4-[(5-bromo-pyrimidin-2-yl)-methyl-amino]-cyclohexyl}-prop-2-ynyl ester	Ethyl-(2-hydroxy-ethyl)-amine
2.5	trans-{(5-Bromo-pyrimidin-2-yl)-methyl-[4-(3-piperidin-1-yl-prop-1-	391, 1Br		trans-Methanesulfonic acid 3-{4-[(5-bromo-pyrimidin-2-yl)-methyl-amino]-	Piperidine

-continued

Example	Compound	MS MH ⁺	Mp ° C.	Mesylate/Chloride/ pyridinium-derivatives	Secondary amine
2.6	ynyl)-cyclohexyl]- amine] trans-{(5-Bromo- pyrimidin-2-yl)-[4-(3- diethylamino-prop-1- ynyl)-cyclohexyl]- methyl-amine]	379, 1Br		cyclohexyl)-prop-2-ynyl ester trans-Methanesulfonic acid 3-{4-[(5-bromo- pyrimidin-2-yl)- methyl-amino]- cyclohexyl)-prop-2-ynyl ester	Diethylamine
2.7	trans-[4-(3- Dimethylamino-prop- 1-ynyl)-cyclohexyl]- methyl-pyrimidin-2-yl- amine	273		trans-Methanesulfonic acid 3-{4-(methyl- pyrimidin-2-yl-amino)- cyclohexyl)-prop-2-ynyl ester	Dimethylamine, 33% in EtOH 5.6 M
2.8	trans-(6-Chloro- pyridazin-3-yl)-[4-(3- dimethylamino-prop- 1-ynyl)-cyclohexyl]- methyl-amine	307, 1Cl	90- 94, dec.	trans-Methanesulfonic acid 3-{4-[(6-chloro- pyridazin-3-yl)-methyl- amino]-cyclohexyl)- prop-2-ynyl ester	Dimethylamine, 33% in EtOH 5.6 M
2.9	trans-2-{(3-{4-[(6- Chloro-pyridazin-3- yl)-methyl-amino]- cyclohexyl)-prop-2- ynyl)-ethyl-amino]- ethanol *	351, 1Cl		trans-Methanesulfonic acid 3-{4-[(6-chloro- pyridazin-3-yl)-methyl- amino]-cyclohexyl)- prop-2-ynyl ester	Ethyl-(2-hydroxy- ethyl)-amine
2.10	trans-(6-Chloro- pyridazin-3-yl)-methyl- [4-(3-piperidin-1-yl- prop-1-ynyl)- cyclohexyl]-amine	347, 1Cl		trans-Methanesulfonic acid 3-{4-[(6-chloro- pyridazin-3-yl)-methyl- amino]-cyclohexyl)- prop-2-ynyl ester	Piperidine
2.11	trans-(6-Chloro- pyridazin-3-yl)-methyl- [4-(3-pyrrolidin-1-yl- prop-1-ynyl)- cyclohexyl]-amine	333, 1Cl		trans-Methanesulfonic acid 3-{4-[(6-chloro- pyridazin-3-yl)-methyl- amino]-cyclohexyl)- prop-2-ynyl ester	Pyrrolidine
2.12	trans-(6-Chloro- pyridazin-3-yl)-[4-(3- diethylamino-prop-1- ynyl)-cyclohexyl]- methyl-amine	335, 1Cl	51- 53, dec.	trans-Methanesulfonic acid 3-{4-[(6-chloro- pyridazin-3-yl)-methyl- amino]-cyclohexyl)- prop-2-ynyl ester	Diethylamine
2.13	trans-(6-Chloro- pyridazin-3-yl)-methyl- [4-{3-(methyl-propyl- amino)-prop-1-ynyl]- cyclohexyl]-amine	335, 1Cl		trans-Methanesulfonic acid 3-{4-[(6-chloro- pyridazin-3-yl)-methyl- amino]-cyclohexyl)- prop-2-ynyl ester	N-Methylpropyl- amine
2.14	trans-(5-Chloro- pyrimidin-2-yl)-[4-(3- dimethylamino-prop- 1-ynyl)-cyclohexyl]- methyl-amine	307, 1Cl		trans-Methanesulfonic acid 3-{4-[(5-chloro- pyrimidin-2-yl)- methyl-amino]- cyclohexyl)-prop-2-ynyl ester	Dimethylamine, 33% in EtOH 5.6 M
2.15	trans-2-{(3-{4-[(5- Chloro-pyrimidin-2- yl)-methyl-amino]- cyclohexyl)-prop-2- ynyl)-ethyl-amino]- ethanol *	351, 1Cl		trans-Methanesulfonic acid 3-{4-[(5-chloro- pyrimidin-2-yl)- methyl-amino]- cyclohexyl)-prop-2-ynyl ester	Ethyl-(2-hydroxy- ethyl)-amine
2.16	trans-(5-Chloro- pyrimidin-2-yl)- methyl-[4-(3- piperidin-1-yl-prop-1- ynyl)-cyclohexyl]- amine	347, 1Cl	58- 60° C. dec.	trans-Methanesulfonic acid 3-{4-[(5-chloro- pyrimidin-2-yl)- methyl-amino]- cyclohexyl)-prop-2-ynyl ester	Piperidine
2.17	trans-(5-Bromo- pyridin-2-yl)-[4-(3- dimethylamino-prop- 1-ynyl)-cyclohexyl]- methyl-amine	350, 1Br		trans-Methanesulfonic acid 3-{4-[(5-bromo- pyridin-2-yl)-methyl- amino]-cyclohexyl)- prop-2-ynyl ester	Dimethylamine, 33% in EtOH 5.6 M
2.18	trans-2-{(3-{4-[(5- Bromo-pyridin-2-yl)- methyl-amino]- cyclohexyl)-prop-2- ynyl)-ethyl-amino]- ethanol *	394, 1 Br		trans-Methanesulfonic acid 3-{4-[(5-bromo- pyridin-2-yl)-methyl- amino]-cyclohexyl)- prop-2-ynyl ester	Ethyl-(2-hydroxy- ethyl)-amine

-continued

Example	Compound	MS MH ⁺	Mp ° C.	Mesylate/Chloride/ pyridinium-derivatives	Secondary amine
2.19	trans-[4-(3-Dimethylamino-prop-1-ynyl)-cyclohexyl]-methyl-pyridin-2-yl-amine	272		trans-Methanesulfonic acid 3-[4-(methyl-pyridin-2-yl-amino)-cyclohexyl]-prop-2-ynyl ester	Dimethylamine, 33% in EtOH 5.6 M
2.20	trans-[4-(3-Dimethylamino-prop-1-ynyl)-cyclohexyl]-methyl-pyrazin-2-yl-amine	273	55-57	trans-Methanesulfonic acid 3-[4-(methyl-pyrazin-2-yl-amino)-cyclohexyl]-prop-2-ynyl ester	Dimethylamine, 33% in EtOH 5.6 M
2.21	trans-6-(Methyl-[4-(3-(methyl-propyl-amino)-prop-1-ynyl)-cyclohexyl]-amino)-nicotinonitrile	325		trans-Methanesulfonic acid 3-[4-(5-cyanopyridin-2-yl)-methyl-amino]-cyclohexyl]-prop-2-ynyl ester	N-Methylpropyl-amine
2.22	trans-6-[Methyl-[4-(3-piperidin-1-yl-prop-1-ynyl)-cyclohexyl]-amino]-nicotinonitrile	337	114-116	trans-Methanesulfonic acid 3-[4-(5-cyanopyridin-2-yl)-methyl-amino]-cyclohexyl]-prop-2-ynyl ester	Piperidine
2.23	trans-6-[4-(3-Dimethylamino-prop-1-ynyl)-cyclohexyl]-methyl-aminol-nicotinonitrile	297		trans-Methanesulfonic acid 3-[4-(5-cyanopyridin-2-yl)-methyl-amino]-cyclohexyl]-prop-2-ynyl ester	Dimethylamine, 33% in EtOH 5.6 M
2.24	trans-(5-Ethyl-pyrimidin-2-yl)-methyl-[4-(3-piperidin-1-yl-prop-1-ynyl)-cyclohexyl]-amine	341		trans-1-(3-[4-(5-Ethyl-pyrimidin-2-yl)-methyl-amino]-cyclohexyl)-prop-2-ynyl-pyridinium; methanesulfonate	Piperidine
2.25	trans-[4-(3-Dimethylamino-prop-1-ynyl)-cyclohexyl]-(5-ethyl-pyrimidin-2-yl)-methyl-amine	301		trans-1-(3-[4-(5-Ethyl-pyrimidin-2-yl)-methyl-amino]-cyclohexyl)-prop-2-ynyl-pyridinium; methanesulfonate	Dimethylamine, 33% in EtOH 5.6 M
2.26	trans-[4-(3-Dimethylamino-prop-1-ynyl)-cyclohexyl]-methyl-(6-methyl-pyridazin-3-yl)-amine	287		trans-[4-(3-Chloro-prop-1-ynyl)-cyclohexyl]-methyl-(6-methyl-pyridazin-3-yl)-amine	Dimethylamine, 33% in EtOH 5.6 M
2.27	trans-2-[Ethyl-(3-[4-[methyl-(6-methyl-pyridazin-3-yl)-amino]-cyclohexyl]-prop-2-ynyl)-aminol-ethanol	331		trans-[4-(3-Chloro-prop-1-ynyl)-cyclohexyl]-methyl-(6-methyl-pyridazin-3-yl)-amine	Ethyl-(2-hydroxy-ethyl)-amine

Example 3

[0282] 3.1

[0283] A suspension of 3.4 g (12.72 mmol) of trans-[4-(3-Hydroxy-prop-1-ynyl)-cyclohexyl]-methyl-carbamic acid tert-butyl ester in 125 ml ethanol and 810 mg of PtO₂·H₂O was hydrogenated (1 atm) for 7 h. The reaction was filtered (Celite) and evaporated to give 3.5 g (quantitative) of trans-[4-(3-Hydroxy-propyl)-cyclohexyl]-methyl-carbamic acid tert-butyl ester, MS: 271 (M).

[0284] 3.2

[0285] In analogy to example 1.6, trans-[4-(3-Hydroxy-propyl)-cyclohexyl]-methyl-carbamic acid tert-butyl gave trans-3-(4-Methylamino-cyclohexyl)-propan-1-ol, MS: 172 (MH⁺).

[0286] 3.3

[0287] In analogy to example 1.7, trans-3-(4-Methylamino-cyclohexyl)-propan-1-ol gave trans-3-[4-(5-

Bromo-pyrimidin-2-yl)-methyl-amino]-cyclohexyl]-propan-1-ol, MS: 328 (MH⁺, 1Br).

[0288] 3.4

[0289] In analogy to example 1.17, trans-3-[4-[(5-Bromopyrimidin-2-yl)-methyl-amino]-cyclohexyl]-propan-1-ol gave after 5 h trans-Methanesulfonic acid 3-[4-[(5-bromopyrimidin-2-yl)-methyl-amino]-cyclohexyl]-propyl ester, MS: 406 (MH⁺, 1Br).

Example 4

[0290] A solution of 209 mg (corresponding to 0.50 mmol) of crude trans-Methanesulfonic acid 3-[4-[(5-bromopyrimidin-2-yl)-methyl-amino]-cyclohexyl]-propyl ester in 5 ml of methanol was treated with 0.89 ml (5 mmol) Dimethylamine (33% in EtOH, 5.6M) and stirred over night at RT. After the addition of 0.45 ml (2.5 mmol) Dimethylamine (33% in EtOH, 5.6M), the reaction was stirred for 66 h, then heated at 70° C. for 2 h, cooled, evaporated and the

residue extracted with aqueous saturated $\text{NaHCO}_3/\text{Et}_2\text{O}$ (3x). The organic phase was dried with Na_2SO_4 , filtered and evaporated. Purification by flash column chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 97:3 to 94:6) gave 157 mg (88%) of trans-(5-Bromo-pyrimidin-2-yl)-[4-(3-dimethylamino-propyl)-cyclohexyl]-methyl-amine, MS: 355 (MH^+ , 1Br).

[0291] The following compounds were prepared from the corresponding mesylates and secondary amines. (In case the reaction was not finished, it was heated at reflux until completion of the reaction):

Example	Compound	MS MH^+	Mesylate	Secondary amine
4.1	trans-{4-[3-(Allyl-methyl-amino)-propyl]-cyclohexyl}-(5-bromo-pyrimidin-2-yl)-methyl-amine	381, 1Br	trans-Methanesulfonic acid 3-{4-[(5-bromo-pyrimidin-2-yl)-methyl-amino]-cyclohexyl}-propyl ester	N-Allylmethyl-amine
4.2	trans-(5-Bromo-pyrimidin-2-yl)-methyl-{4-[3-(methyl-propyl-amino)-propyl]-cyclohexyl}-amine	383, 1Br	trans-Methanesulfonic acid 3-{4-[(5-bromo-pyrimidin-2-yl)-methyl-amino]-cyclohexyl}-propyl ester	N-Methylpropyl-amine
4.3	trans-(5-Bromo-pyrimidin-2-yl)-4-{3-[ethyl-(2-methoxy-ethyl)-amino]-propyl}-cyclohexyl)-methyl-amine	413, 1Br	trans-Methanesulfonic acid 3-{4-[(5-bromo-pyrimidin-2-yl)-methyl-amino]-cyclohexyl}-propyl ester	N-(2-Methoxyethyl)ethylamine

Example 5

[0292] 5.1

[0293] A solution of 10.0 g (25.2 mmol) of trans-[4-(2,2-Dibromo-vinyl)-cyclohexyl]-methyl-carbamic acid tert-butyl ester in 400 ml THF was treated at -78°C . with 33.0 ml (68.3 mmol) of BuLi (ca 1.6 M in hexane) and stirred for 2 h, then 27.8 ml (230.4 mmol) of DMPU were added and 10 min later 19.0 ml (125.9 mmol) of 2-(2-bromoethoxy)tetrahydro-2H-pyran dissolved in 20 ml were dropped in during 20 min. The reaction was warmed up to RT and stirred over night (approx. 16 h). An aqueous solution of saturated NH_4Cl was added and the mixture was extracted with Et_2O (3x). The organic phase was washed with H_2O (2x), aqueous 10% NaCl and dried with Na_2SO_4 , filtered and evaporated to give after flash column chromatography on silica gel (hexane/EtOAc 19:1 to 3:1) 3.5 g (38%) of trans-Methyl-{4-[4-(tetrahydro-pyran-2-yloxy)-but-1-ynyl]-cyclohexyl}-carbamic acid tert-butyl ester, MS: 366 (MH^+).

[0294] 5.2

[0295] A solution of 3.45 g (9.44 mmol) of trans-Methyl-{4-[4-(tetrahydro-pyran-2-yloxy)-but-1-ynyl]-cyclohexyl}-carbamic acid tert-butyl ester and 0.7 g (2.83 mmol) of pyrimidium toluene-4-sulfonate in 25 ml MeOH was stirred at 55°C . for 1.5 h. The reaction was partitioned between aqueous solution of 10% $\text{KHSO}_4/\text{Et}_2\text{O}$ (3x). The organic phases were washed with aqueous saturated NaHCO_3 , 10% NaCl, dried over Na_2SO_4 and evaporated to give 2.85 g (quantitative) of trans-[4-(4-Hydroxy-but-1-ynyl)-cyclohexyl]-methyl-carbamic acid tert-butyl ester, MS: 281 (M).

[0296] 5.3

[0297] In analogy to example 1.6, trans-[4-(4-Hydroxy-but-1-ynyl)-cyclohexyl]-methyl-carbamic acid tert-butyl ester with TFA was converted to trans-4-(4-Methylamino-cyclohexyl)-but-3-yn-1-ol, MS: 182 (MH^+).

[0298] 5.4

[0299] A mixture of 1.06 g (5.85 mmol) trans-4-(4-Methylamino-cyclohexyl)-but-3-yn-1-ol, 1.67 g (7.02 mmol) of 2,5-dibromo-pyrimidine [Brown, Desmond J.; Arantz, B.

W., Pyrimidine reactions. XXII. Relative reactivities of corresponding chloro-, bromo-, and iodopyrimidines in aminolysis. J. Chem. Soc. C (1971), Issue 10, 1889-91] and 3.38 ml (19.88 mmol) N-ethyl-diisopropylamine were heated for 2 h at 85°C ., diluted with 1 ml DMA and heated for 3.5 h at 85°C . The reaction was cooled, evaporated and partitioned between aqueous saturated $\text{NaHCO}_3/\text{Et}_2\text{O}$ (3x). The organic phases were washed with aqueous 10% NaCl, dried (Na_2SO_4) and evaporated. Flash chromatography on silica gel (hexane/EtOAc 9:1 to 1:1) gave 1.37 g (69%) of trans-4-{4-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-cyclohexyl}-but-3-yn-1-ol, MS: 338 (MH^+ , 1Br).

[0300] 5.5

[0301] In analogy to example 1.17, trans-4-{4-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-cyclohexyl}-but-3-yn-1-ol was converted to trans-Methanesulfonic acid 4-{4-[(5-bromo-pyrimidin-2-yl)-methyl-amino]-cyclohexyl}-but-3-ynyl ester, MS: 416 (MH^+ , 1Br).

Example 6

[0302] 6.1

[0303] A solution of 211 mg (0.51 mmol) of crude trans-Methanesulfonic acid 4-{4-[(5-bromo-pyrimidin-2-yl)-methyl-amino]-cyclohexyl}-but-3-ynyl ester in 5 ml of methanol was treated with 0.91 ml (5.1 mmol) Dimethylamine (33% in EtOH, 5.6M) and heated at 65°C . for 4 h. After cooling and evaporation, the residue was extracted with aqueous saturated $\text{NaHCO}_3/\text{Et}_2\text{O}$ (3x). The organic phase was dried (Na_2SO_4), filtered and evaporated. Purification by flash column chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 99:1 to 95:5) gave 141 mg (76%) of trans-(5-Bromo-pyrimidin-2-yl)-[4-(4-dimethylamino-but-1-ynyl)-cyclohexyl]-methyl-amine, MS: 365 (MH^+ , 1Br).

[0304] 6.2

[0305] In analogy to example 6.1, trans-Methanesulfonic acid 4-{4-[(5-bromo-pyrimidin-2-yl)-methyl-amino]-cyclohexyl}-but-3-ynyl ester and piperidine gave after 4.5 h at 65° C., trans-(5-Bromo-pyrimidin-2-yl)-methyl-[4-(4-piperidin-1-yl-but-1-ynyl)-cyclohexyl]-amine, MS: 405 (MH⁺, 1Br).

Example 7

[0306] 7.1

[0307] In analogy to example 3.1, trans-[4-(4-Hydroxy-but-1-ynyl)-cyclohexyl]-methyl-carbamic acid tert-butyl ester was converted to trans-[4-(4-Hydroxy-butyl)-cyclohexyl]-methyl-carbamic acid tert-butyl ester, MS: 286 (MH⁺).

[0308] 7.2

[0309] In analogy to example 1.6, trans-[4-(4-Hydroxy-butyl)-cyclohexyl]-methyl-carbamic acid tert-butyl ester was converted to trans-4-(4-Methylamino-cyclohexyl)-butan-1-ol, MS: 186 (MH⁺).

[0310] 7.3

[0311] In analogy to example 1.7, trans-4-(4-Methylamino-cyclohexyl)-butan-1-ol and 2,5-dibromo-pyrimidine was converted to trans-4-{4-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-cyclohexyl}-butan-1-ol, MS: 342 (MH⁺, 1Br).

[0312] 7.4

[0313] In analogy to example 1.17, trans-4-{4-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-cyclohexyl}-butan-1-ol yielded after 2.5 h trans-Methanesulfonic acid 4-{4-[(5-bromo-pyrimidin-2-yl)-methyl-amino]-cyclohexyl}-butyl ester, MS: 420 (MH⁺, 1Br).

Example 8

[0314] 8.1

[0315] In analogy to example 6.1, trans-Methanesulfonic acid 4-{4-[(5-bromo-pyrimidin-2-yl)-methyl-amino]-cyclohexyl}-butyl ester and Dimethylamine (33% in EtOH, 5.6M) gave after 4 h at 65° C., trans-(5-Bromo-pyrimidin-2-yl)-[4-(4-dimethylamino-butyl)-cyclohexyl]-methyl-amine, MS: 369 (MH⁺, 1Br).

[0316] 8.2

[0317] In analogy to example 6.1, trans-Methanesulfonic acid 4-{4-[(5-bromo-pyrimidin-2-yl)-methyl-amino]-cyclohexyl}-butyl ester and piperidine gave after 7 h at 65° C., trans-(5-Bromo-pyrimidin-2-yl)-methyl-[4-(4-piperidin-1-yl-butyl)-cyclohexyl]-amine, MS: 409 (MH⁺, 1Br).

Example 9

[0318] 9.1

[0319] A well stirred solution of 100 g (774 mmol) of cis-4-Methylamino-cyclohexanol [Schut, Robert N. Analgesic 3-(methylamino)-1,2,3,4-tetrahydrocarbazole from 4-(methylamino)cyclohexanone. Fr. (1968), 3 pp. FR 1515629 19680301] in 775 ml EtOAc was treated with 1.55 l of aqueous 1M NaHCO₃ and with 110 ml (774 mmol) of benzyl chloroformate (30 min, Tmax 30° C.). The phases

were separated after 2 h at RT. The aqueous phase was extracted (EtOAc), the organic phases were dried (Na₂SO₄), filtered and evaporated. Purification by column chromatography on silica gel (hexane/EtOAc 2:1) gave 139 g (68%) of cis-(4-Hydroxy-cyclohexyl)-methyl-carbamic acid benzyl ester, MS: 263 (M).

[0320] 9.2

[0321] A solution of 2.63 g (10 mmol) of cis-(4-Hydroxy-cyclohexyl)-methyl-carbamic acid benzyl ester in 16 ml CH₂Cl₂ was treated with a solution 0.24 g (2 mmol) of KBr and 0.28 g (3.33 mmol) of NaHCO₃ in 5 ml of water. The suspension was cooled (0-5° C.) and 8 mg (0.05 mmol) of TEMPO and then 5.7 ml (12.5 mmol) of NaOCl (13%, 2.18 M in water) were added during 20 min. After 1 h at this temperature, again 8 mg (0.05 mmol) of TEMPO and then 2.85 ml (6.25 mmol) of NaOCl (13%, 2.18 M in water) were added. After 1 h, 5 ml of 1M sodium thiosulfate solution was added. The aqueous phase was extracted with CH₂Cl₂ (2x), the organic phase was dried (Na₂SO₄), filtered and evaporated to give 2.57 g (99%) of Methyl-(4-oxo-cyclohexyl)-carbamic acid benzyl ester, MS: 261 (M).

[0322] 9.3

[0323] A suspension of 749.88 g (2187.5 mmol) (methoxymethyl)triphenylphosphonium chloride in 2.5 l THF was cooled (-10° C.) and deprotonated with 245.5 g (2187.5 mmol) potassium t-butoxide. The dark red solution was stirred at 0-5° C. for 0.5 h, cooled (-20° C.) and 457.32 g (261.33 mmol) of Methyl-(4-oxo-cyclohexyl)-carbamic acid benzyl ester in 1.25 l THF were dropped in (1.25 h). After 1.3 h at RT, the reaction was treated with 1.75 l aqueous 1M NaHCO₃ and stirred for 45 min. The phases were separated, the aqueous phase was extracted with TBME (700 ml), the organic phase was dried (Na₂SO₄), filtered and evaporated. The residue was suspended in hexane (5 l), cooled (0° C.), filtered and evaporated to give 495.2 g (98%) of (4-Methoxymethylene-cyclohexyl)-methyl-carbamic acid benzyl ester, MS: 289 (M).

[0324] 9.4

[0325] A solution of 495 g (1710.6 mmol) of (4-Methoxymethylene-cyclohexyl)-methyl-carbamic acid benzyl ester in 1.7 l THF was treated at RT with 3.42 l of aqueous 1N HCl and heated at reflux for 2 h. The reaction was cooled to RT and extracted with TBME (1.7 and 0.9 l). The organic phase was washed with aqueous 1M NaHCO₃, dried (Na₂SO₄), filtered and evaporated to give 457.4 (97%) of crude (4-Formyl-cyclohexyl)-methyl-carbamic acid benzyl ester (trans:cis ca 70:30).

[0326] A solution of 327 g (1188 mmol) of crude (4-Formyl-cyclohexyl)-methyl-carbamic acid benzyl ester in 1.64 l TBME was added at RT to a solution of 451.5 g (2375 mmol) of disodium pyrosulfite in 1.64 l water. The reaction was stirred for 15 h, filtered and washed (1.1 l TBME) to give 191.7 g (45%) of the sodium salt of [4-(Benzyloxycarbonyl-methyl-amino)-cyclohexyl]-hydroxy-methanesulfonic acid (trans:cis 95:5). This compound was suspended in 0.5 l TBME and 1.01 l aqueous 1M Na₂CO₃ and stirred for 1 h at RT. The phases were separated, the aqueous phase was extracted with TBME (1 l), the organic phase was dried (Na₂SO₄), filtered and evaporated to give 128 g (36% over the two steps) of trans-(4-Formyl-cyclohexyl)-methyl-carbamic acid benzyl ester (trans:cis 99:1), MS: 275 (M).

[0327] 9.5

[0328] A suspension of 128.6 g (375 mmol) of (methoxymethyl)triphenylphosphonium chloride in 540 ml THF was treated at -8°C . with 43.1 g (375 mmol) potassium tert-butoxide. The red solution was stirred 30 min at 0°C . and cooled (-20°C .), then 82.6 g (300 mmol) of trans-(4-Formyl-cyclohexyl)-methyl-carbamic acid benzyl ester in 240 ml THF were dropped in (60 min). The reaction was warmed to RT and stirred for 2 h, washed with aqueous saturated NaHCO_3 (540 ml). The water phase was extracted with 0.5 l TBME, the combined organic phases were oxidized with 16 ml of hydrogen peroxide solution (35%), mixed with water (150 ml). The organic solvent was evaporated, the residue was extracted with MeOH (350 ml)/hexane (2x2000 ml). The hexane was washed twice with 500 ml MeOH/water (7/3), dried (Na_2SO_4) and evaporated to give 81.7 g (90%) of trans-(2E/Z) [4-(2-Methoxy-vinyl)-cyclohexyl]-methyl-carbamic acid benzyl ester, MS: 303(M).

[0329] 9.6

[0330] In analogy to example 9.4, trans-(2E/Z) [4-(2-Methoxy-vinyl)-cyclohexyl]-methyl-carbamic acid benzyl ester gave after 1 h reflux, trans-Methyl-[4-(2-oxo-ethyl)-cyclohexyl]-carbamic acid benzyl ester, MS: 290 (MH^+).

[0331] 9.7

[0332] A suspension of 77.4 g (267.4 mmol) of trans-Methyl-[4-(2-oxo-ethyl)-cyclohexyl]-carbamic acid benzyl ester, 63.86 g (292.6 mmol) of di-tert-butyl dicarbonate and 7.7 g of Pd/C 10% in 775 ml EtOAc was hydrogenated (1 atm) at 38°C . for 48 h (during the day, every hour, the hydrogen was exchanged). The reaction was filtered (Celite) and evaporated to give after flash silica gel column (hexane/EtOAc 4:1) 38.4 g (56%) of trans-Methyl-[4-(2-oxo-ethyl)-cyclohexyl]-carbamic acid tert-butyl ester, MS: 255 (M).

[0333] 9.8

[0334] In analogy to example 1.4, trans-Methyl-[4-(2-oxo-ethyl)-cyclohexyl]-carbamic acid tert-butyl ester was converted to trans-[4-(3,3-Dibromo-allyl)-cyclohexyl]-methyl-carbamic acid tert-butyl ester, MS: 352 (M-Butene, 2Br).

[0335] 9.9

[0336] In analogy to example 1.5, trans-[4-(3,3-Dibromo-allyl)-cyclohexyl]-methyl-carbamic acid tert-butyl ester was converted to trans-[4-(4-Hydroxy-but-2-ynyl)-cyclohexyl]-methyl-carbamic acid tert-butyl ester, MS: 281 (M).

[0337] 9.10

[0338] In analogy to example 1.6, trans-[4-(4-Hydroxy-but-2-ynyl)-cyclohexyl]-methyl-carbamic acid tert-butyl ester was converted to trans-4-(4-Methylamino-cyclohexyl)-but-2-yn-1-ol, MS: 182 (MH^+).

[0339] 9.11

[0340] In analogy to example 1.15, trans-4-(4-Methylamino-cyclohexyl)-but-2-yn-1-ol and 3,6-dichloropyridazine gave, with no NaI after 6 h at 80°C . and 3/4 h at 120°C . in the microwave oven, trans-4-[4-(6-Chloro-pyridazin-3-yl)-methyl-amino]-cyclohexyl]-but-2-yn-1-ol, MS: 294 (MH^+ , 1Cl).

[0341] 9.12

[0342] In analogy to example 1.15, trans-4-(4-Methylamino-cyclohexyl)-but-2-yn-1-ol and 1.2 eq of 2,5-dibromo-pyrimidine [Brown, Desmond J.; Arantz, B. W., Pyrimidine reactions. XXII. Relative reactivities of corresponding chloro-, bromo-, and iodopyrimidines in aminolysis. J. Chem. Soc. C (1971), Issue 10, 1889-91] gave, with no NaI after 6 h at 80°C . and 1/4 h at 120°C . in the microwave oven, trans-4-[4-(5-Bromo-pyrimidin-2-yl)-methyl-amino]-cyclohexyl]-but-2-yn-1-ol, MS: 338 (MH^+ , 1Br).

[0343] 9.13

[0344] A solution of 1.08 g (3.68 mmol) of trans-4-[4-(6-Chloro-pyridazin-3-yl)-methyl-amino]-cyclohexyl]-but-2-yn-1-ol in 30 ml CH_2Cl_2 was treated at 0°C . with 0.31 ml (4.04 mmol) methanesulfonylchloride and 0.64 ml (5.51 mmol) 2,6-lutidine. The reaction was stirred for 46 h at room temperature, water (4 ml) was added and stirred for 5 min. After extraction with aqueous saturated $\text{NaHCO}_3/\text{Et}_2\text{O}$ (3x), the organic phase was washed with aqueous 10% NaCl, dried over Na_2SO_4 and evaporated to yield 1.45 g of crude trans-Methanesulfonic acid 4-[4-(6-chloro-pyridazin-3-yl)-methyl-amino]-cyclohexyl]-but-2-ynyl ester, MS: 372 (MH^+ , 1Cl).

[0345] 9.14

[0346] In analogy to example 9.13, trans-4-[4-(5-Bromopyrimidin-2-yl)-methyl-amino]-cyclohexyl]-but-2-yn-1-ol was converted to trans-methanesulfonic acid 4-[4-(5-bromo-pyrimidin-2-yl)-methyl-amino]-cyclohexyl]-but-2-ynyl ester, MS: 416 (MH^+ , 1Br).

Example 10

[0347] In analogy to example 2, the following compounds were prepared from the corresponding mesylates and secondary amines:

Example	Compound	MS MH^+	Mesylate	Secondary amine
10.1	trans-(6-Chloro-pyridazin-3-yl)-[4-(4-dimethylamino-but-2-ynyl)-cyclohexyl]-methyl-amine	321, 1Cl	trans-Methanesulfonic acid 4-[4-(6-chloro-pyridazin-3-yl)-methyl-amino]-cyclohexyl]-but-2-ynyl ester	Dimethylamine, 33% in EtOH 5.6 M
10.2	trans-(6-Chloro-pyridazin-3-yl)-methyl-[4-(4-piperidin-1-yl-but-2-ynyl)-cyclohexyl]-amine	361, 1Cl	trans-Methanesulfonic acid 4-[4-(6-chloro-pyridazin-3-yl)-methyl-amino]-cyclohexyl]-but-2-ynyl ester	Piperidine

-continued

Example	Compound	MS MH ⁺	Mesylate	Secondary amine
10.3	trans-(5-Bromo-pyrimidin-2-yl)-[4-(4-dimethylamino-but-2-ynyl)-cyclohexyl]-methyl-amine	365, 1Br	trans-methanesulfonic acid 4-{4-[(5-bromo-pyrimidin-2-yl)-methyl-amino]-cyclohexyl}-but-2-ynyl ester	Dimethylamine, 33% in EtOH 5.6 M
10.4	trans-(5-Bromo-pyrimidin-2-yl)-methyl-[4-(4-piperidin-1-yl-but-2-ynyl)-cyclohexyl]-amine	395, 1Br	trans-methanesulfonic acid 4-{4-[(5-bromo-pyrimidin-2-yl)-methyl-amino]-cyclohexyl}-but-2-ynyl ester	Piperidine

Example 11

[0348] 11.1

[0349] To a dry-ice cooled solution of 30.0 g (208 mmol) of trans-(4-hydroxymethyl-cyclohexyl)-methanol in 450 ml tetrahydrofuran was dropped at -60° C. to -67° C., within 30 minutes, 130 ml (208 mmol) of 1.6 M butyllithium solution (1.6 M in hexane). After stirring for 30 minutes at -78° C., 32.3 g (208 mmol) of tert-butyl-dimethyl-chlorosilane was added within 10 minutes. After 15 minutes at -65° C., the reaction was stirred over night at room temperature and then partitioned between Et₂O, 1N hydrogen chloride solution and water. The organic layer was dried over magnesium sulfate, concentrated under reduced pressure and the residue then chromatographed on silica gel with a 3:1 v/v mixture of hexane and ethylacetate as the eluent giving 27.7 g (51%) of pure trans-[4-(tert-butyl-dimethyl-silanyloxymethyl)-cyclohexyl]-methanol as colorless viscous oil, MS: 259 (MH⁺).

[0350] 11.2

[0351] To an ice-cooled solution of 27.6 g (107 mmol) of trans-[4-(tert-butyl-dimethyl-silanyloxymethyl)-cyclohexyl]-methanol and 9.99 ml (128 mmol) of methanesulfonyl chloride in 350 ml of dichloromethane was added under stirring at 0-10° C. 29.6 ml (213 mmol) of triethylamine within 20 minutes. The reaction-mixture was stirred for 1 hour at room temperature. It was then partitioned between dichloromethane, 1N HCl and water. The dichloromethane-phase was dried over magnesium sulfate and concentrated to yield 38.2 g crude trans-methanesulfonic acid 4-(tert-butyl-dimethyl-silanyloxymethyl)-cyclohexylmethyl ester as colorless viscous oil, MS: 354 (M+NH₄⁺).

[0352] 11.3

[0353] 38.2 g of crude trans-methanesulfonic acid 4-(tert-butyl-dimethyl-silanyloxymethyl)-cyclohexylmethyl ester and 16.7 g (340 mmol) of sodium cyanide dissolved in 380 ml of N,N-dimethylformamide were stirred for 2 hours at 80° C. After cooling the reaction mixture down to room temperature, it was partitioned between Et₂O and water. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure and the residue then chromatographed on silica gel with a 9:1 v/v mixture of hexane and ethylacetate as the eluent giving 24.2 g (78% over two steps) of pure trans-[4-(tert-butyl-dimethyl-silanyloxymethyl)-cyclohexyl]-acetonitrile as colorless viscous oil, MS: 290 (MNa⁺).

[0354] 11.4

[0355] A solution of 24.2 g (90.5 mmol) of trans-[4-(tert-butyl-dimethyl-silanyloxymethyl)-cyclohexyl]-acetonitrile, of 22 ml (270 mmol) chloroform and of 2.4 g PtO₂·H₂O (Degussa 223) in 250 ml ethanol was stirred at room temperature for 20 hours under a hydrogen atmosphere. The catalyst was then removed by filtration and the solvent evaporated under reduced pressure giving 17.1 g (97%) of pure trans-[4-(2-amino-ethyl)-cyclohexyl]-methanol HCl-salt as colorless solid, MS: 158 (MH⁺).

[0356] 11.5

[0357] In analogy to example 5.4, trans-[4-(2-amino-ethyl)-cyclohexyl]-methanol HCl-salt with 5.4 eq N-ethyl-diisopropylamine and 1.2 eq 2,5-dibromo-pyrimidine in DMA for 7.5 h at 85° C. gave trans-[4-[2-(5-Bromo-pyrimidin-2-ylamino)-ethyl]-cyclohexyl]-methanol, mp: 151.7-153.4° C.; MS: 314 (MH⁺, 1Br).

[0358] 11.6

[0359] A solution of 481 mg (1.53 mmol) of trans-[4-[2-(5-Bromo-pyrimidin-2-ylamino)-ethyl]-cyclohexyl]-methanol in 14 ml CH₂Cl₂ was treated at 0 C with 0.13 ml (1.68 mmol) methanesulfonylchloride and 0.27 ml (2.30 mmol) 2,6-lutidine. The reaction was stirred for 20 h at room temperature, water (2 ml) was added and stirred for 5 min. After extraction with aqueous saturated NaHCO₃/Et₂O(3x), the organic phase was washed with aqueous 10% NaCl, dried over Na₂SO₄ and evaporated to yield 970 mg of crude trans-Methanesulfonic acid 4-[2-(5-bromo-pyrimidin-2-ylamino)-ethyl]-cyclohexylmethyl ester, MS: 392 (MH⁺, 1Br).

[0360] 11.7

[0361] To a solution of 17.6 g (90.9 mmol) trans-[4-(2-amino-ethyl)-cyclohexyl]-methanol HCl-salt and 13.9 ml (100 mmol) triethylamine in 120 ml dichloromethane was added under stirring within 10 minutes at room temperature a solution of 21.8 g (100 mmol) of di-tert-butyl-dicarbonate in 70 ml of dichloromethane. After stirring for 3 hours at room temperature, the reaction-mixture was partitioned between dichloromethane, 1N hydrogen chloride solution and water. Then, the dichloromethane-phase was dried over magnesium sulfate and concentrated to yield 27.9 g of crude trans-[2-(4-hydroxymethyl-cyclohexyl)-ethyl]-carbamic acid tert-butyl ester as colorless viscous oil, MS: 275 (MNH₄⁺).

[0362] 11.8

[0363] A solution of 27.9 g (86.7 mmol) trans-[2-(4-hydroxymethyl-cyclohexyl)-ethyl]-carbamic acid tert-butyl ester, 41 ml (434 mmol) acetic anhydride and 35 ml (434 mmol) of pyridine in 140 ml of dichloromethane was stirred at room temperature for 16 hours. The reaction-mixture was then taken up in Et₂O and washed with 1N hydrogen chloride solution, sodium hydrogen carbonate solution and water. Then, the Et₂O-phase was dried over magnesium sulfate and concentrated to yield 26.0 g crude trans-acetic acid 4-(2-tert-butoxycarbonylamino-ethyl)-cyclohexylmethyl ester as colorless viscous oil, MS: 200 [(M-(tert-butoxycarbonyl))H⁺].

[0364] 11.9

[0365] To an ice-cooled and stirred solution of the crude 26.0 g trans-acetic acid 4-(2-tert-butoxycarbonylamino-ethyl)-cyclohexylmethyl ester and 5.77 ml (92.6 mmol) methyl iodide in 300 ml of N,N-dimethylformamide was added within 15 minutes 4.04 g (92.58 mmol) sodium hydride (55% in oil). After stirring over night at room temperature, additional 1.65 ml (26.5 mmol) methyl iodide and 1.16 g (26.5 mmol) of sodium hydride were added and the reaction-mixture was then stirred for another 1 hour at room temperature. It was then partitioned between Et₂O, 1N hydrogen chloride solution and water. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure and the residue then chromatographed on silica gel with a 4:1 v/v mixture of hexane and ethylacetate as the eluent giving 18.7 g (68% over 3 steps) of pure trans-acetic acid 4-[2-(tert-butoxycarbonyl-methyl-amino)-ethyl]-cyclohexylmethyl ester as colorless viscous oil, MS: 214 [(M-(tert-butoxycarbonyl)) H⁺].

[0366] 11.10

[0367] To a solution of 18.7 g (59.7 mmol) of trans-acetic acid 4-[2-(tert-butoxycarbonyl-methyl-amino)-ethyl]-cyclohexylmethyl ester in 110 ml of methanol was added 41.25 g (298.5 mmol) of potassium carbonate. The reaction mixture was then stirred for 2 hours at room temperature. The excess of potassium carbonate was removed by filtration and the methanol was removed by evaporation under reduced pressure. The crude residue was partitioned between Et₂O, 1N hydrogen chloride solution and water. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure and the residue then chromatographed on silica gel with a 2:1 v/v mixture of hexane and ethylacetate as the eluent giving 13.9 g (86%) of pure trans-[2-(4-

hydroxymethyl-cyclohexyl)-ethyl]-methyl-carbamic acid tert-butyl ester as colorless viscous oil, MS: 272 (MH⁺).

[0368] 11.11

[0369] A solution of 1.45 g (5.34 mmol) of trans-[2-(4-hydroxymethyl-cyclohexyl)-ethyl]-methyl-carbamic acid tert-butyl ester in 10 ml dioxane was treated at 10° C. with 13.4 ml (53.4 mmol) of HCl in dioxane (4M). After 3.5 h at RT, the reaction was evaporated to give 1.6 g (quantitative) of trans-[4-(2-Methylamino-ethyl)-cyclohexyl]-methanol hydrochloride, MS: 172 (MH⁺).

[0370] 11.12

[0371] In analogy to example 5.4, trans-[4-(2-Methylamino-ethyl)-cyclohexyl]-methanol hydrochloride with 5.4 eq of N-ethyl-diisopropylamine and 1.2 eq of 2,5-dibromopyrimidine [Brown, Desmond J.; Arantz, B. W., Pyrimidine reactions. XXII. Relative reactivities of corresponding chloro-, bromo-, and iodopyrimidines in aminolysis. J. Chem. Soc. C (1971), Issue 10, 1889-91] was converted (½ h at 85° C. with no solvent and 6 h at 85° C. in DMA) to trans-(4-{2-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-ethyl}-cyclohexyl)-methanol, mp: 61-63° C.; MS: 328 (MH⁺, 1Br).

[0372] 11.13

[0373] In analogy to example 11.6, trans-(4-{2-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-ethyl}-cyclohexyl)-methanol gave trans-Methanesulfonic acid 4-{2-[(5-bromopyrimidin-2-yl)-methyl-amino]-ethyl}-cyclohexylmethyl ester, MS: 406 (MH⁺, 1 Br).

Example 12

[0374] A solution of 258 mg (corresponding to 0.41 mmol) of crude trans-Methanesulfonic acid 4-[2-(5-bromopyrimidin-2-ylamino)-ethyl]-cyclohexylmethyl ester in 5 ml of methanol was treated with 0.73 ml (4.1 mmol) Dimethylamine (33% in EtOH, 5.6M) and heated at 65° C. for 4 h, a catalytic amount of NaI was added and heated for 16 h. After cooling and evaporation, the residue was extracted with aqueous saturated NaHCO₃/Et₂O (3x). The organic phase was dried (Na₂SO₄), filtered and evaporated. Purification by flash column chromatography on silica gel (CH₂Cl₂/MeOH 99:1 to 9:1) gave 105 mg (76%) of trans-(5-Bromo-pyrimidin-2-yl)-[2-(4-dimethylaminomethyl-cyclohexyl)-ethyl]-amine, mp: 108.3-109.5° C.; MS: 341 (MH⁺, 1Br).

[0375] The following compounds were prepared from the corresponding mesylates and secondary amines:

Example	Compound	MS MH ⁺	Mp ° C.	Mesylate	Secondary amine
12.1	trans-(5-Bromo-pyrimidin-2-yl)-[2-(4-piperidin-1-ylmethyl-cyclohexyl)-ethyl]-amine	381, 1Br	138- 139	trans-Methanesulfonic acid 4-[2-(5-bromopyrimidin-2-ylamino)-ethyl]-cyclohexylmethyl ester	Piperidine
12.2	trans-(5-Bromo-pyrimidin-2-yl)-[2-(4-dimethylaminomethyl-cyclohexyl)-ethyl]-methyl-amine	355, 1Br	66- 67	trans-Methanesulfonic acid 4-{2-[(5-bromopyrimidin-2-yl)-methyl-amino]-ethyl}-cyclohexylmethyl ester	Dimethylamine, 33% in EtOH 5.6 M

-continued

Example	Compound	MS MH ⁺	Mp ° C.	Mesylate	Secondary amine
12.3	trans-(5-Bromo-pyrimidin-2-yl)-methyl-[2-(4-piperidin-1-ylmethyl-cyclohexyl)-ethyl]-amine	395, 1Br	76– 82 dec.	trans-Methanesulfonic acid 4-{2-[(5-bromo-pyrimidin-2-yl)-methyl-amino]-ethyl}-cyclohexylmethyl ester	Piperidine

Example 13

[0376] 13.1

[0377] In this reaction, the solvents were degassed with argon for 10 minutes. A suspension of 7.3 mg PdCl₂(dppf), of 29.4 mg (0.24 mmol) of 4-pyridylboronic acid and of 70 mg (0.2 mmol) of trans-(5-Bromo-pyrimidin-2-yl)-[4-(3-dimethylamino-prop-1-ynyl)-cyclohexyl]-methyl-amine in 3.5 ml dioxane were treated with 1 ml of an aqueous solution of 2M Na₂CO₃. After 17 h at 85° C., 7 mg of PdCl₂(dppf) were added and the reaction was heated further at 85° C. for 24 h. The mixture was partitioned between aqueous saturated NaHCO₃/Et₂O (3x) and the combined organic phases were extracted with 0.1M HCl. The HCl-phase was adjusted to pH 14 (1 N NaOH) and extracted with Et₂O (3x). The organic phase was washed with 10% NaCl and dried over Na₂SO₄ to yield after purification with flash-chromatography on silica gel (CH₂Cl₂/MeOH 99:1 to 9:1) 9 mg (13%) of trans-[4-(3-Dimethylamino-prop-1-ynyl)-cyclohexyl]-methyl-(5-pyridin-4-yl-pyrimidin-2-yl)-amine, MS: 350 (MH⁺).

[0378] 13.2

[0379] In analogy to example 13.1, trans-(5-Bromo-pyrimidin-2-yl)-[4-(3-dimethylamino-prop-1-ynyl)-cyclohexyl]-methyl-amine and thiophene-3-boronic acid was converted to trans-[4-(3-Dimethylamino-prop-1-ynyl)-cyclohexyl]-methyl-(5-thiophen-3-yl-pyrimidin-2-yl)-amine, MS: 355 (MH⁺).

Example 14

[0380] A solution of 92.1 mg (0.3 mmol) of trans-(6-Chloro-pyridazin-3-yl)-[4-(3-dimethylamino-prop-1-ynyl)-cyclohexyl]-methyl-amine in 0.6 ml DMA was treated with 0.56 ml (3 mmol) of sodium methylate (5.4 M in MeOH) and heated at 80° C. for 54 h. The reaction was extracted with aqueous saturated NaHCO₃/Et₂O (3x). The organic phase was dried (Na₂SO₄), filtered and evaporated. Purification by flash column chromatography on silica gel (CH₂Cl₂/MeOH 99:1 to 97:3) yielded 67 mg (74%) of pure trans-[4-(3-Dimethylamino-prop-1-ynyl)-cyclohexyl]-[6-methoxy-pyridazin-3-yl]-methyl-amine, MS: 303 (MH⁺).

Example 15

[0381] 15.1

[0382] A solution of 81 g (314.77 mmol) trans-4-[(tert-Butoxyformamido)methyl]cyclohexanecarboxylic acid in 4 l CH₂Cl₂ was treated with 50.13 g (503.63 mmol) N,O-dimethyl-hydroxylamine hydrochloride, 55.37 ml (503.63 mmol) N-methylmorpholine and at 0° C. with 78.45 g (409.2 mmol) EDCI and 9.67 g (62.95 mmol) HOBt. The reaction

mixture was stirred 16 h at room temperature, evaporated and extracted with aqueous 10% KHSO₄/Et₂O (3x). The organic phases were washed with aqueous saturated NaHCO₃, 10% NaCl and dried over Na₂SO₄ to yield 100.03 g (quantitative) of trans-[4-(Methoxy-methyl-carbamoyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester, MS: 301 (MH⁺).

[0383] 15.2

[0384] A solution of 95 g (corresponds to 301.26 mmol) of crude trans-[4-(Methoxy-methyl-carbamoyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester in 300 ml of DMA was treated at 0° C. with 19.72 g (451.9 mmol) of NaH (55% in oil) in small portions. The reaction was stirred for 1 h at 0° C., then treated slowly (1.5 h) with 150 ml (2.41 mol) of iodomethane. After the addition of 60 ml of iodomethane (1 h), the reaction started, the addition was stopped and continued after reaction was cooled down again. After warming up to RT over night, the reaction was cooled, neutralized with aqueous 10% KHSO₄ and poured into water/Et₂O (3x). The organic phase was washed with aqueous 10% NaCl, dried over Na₂SO₄ evaporated and purified by flash silica gel column (CH₂Cl₂/EtOAc 9:1 to 1:1) to yield 99 g (quantitative) of trans-[4-(Methoxy-methyl-carbamoyl)-cyclohexylmethyl]-methyl-carbamic acid tert-butyl ester, MS: 315 (MH⁺).

[0385] 15.3

[0386] A solution of 12.25 g (313.11 mmol) LAH in 1.3 l THF was cooled (-50° C.) and treated during 30 min with a solution of 89.5 g (284.64 mmol) of trans-[4-(Methoxy-methyl-carbamoyl)-cyclohexylmethyl]-methyl-carbamic acid tert-butyl ester in 1.3 l THF. After 20 min at this temperature, the reaction was warmed up to 0° C., cooled (-78° C.) and hydrolyzed with a suspension of 90 g MgSO₄·7H₂O, 90 g silicagel in 292 ml aqueous 10% KHSO₄. The cooling bath was removed, THF was added, the mixture was stirred for 30 min and filtered. After evaporation, the residue was dissolved in CH₂Cl₂, dried over Na₂SO₄ and evaporated to yield 90.4 (quantitative) of trans-(4-Formyl-cyclohexylmethyl)-methyl-carbamic acid tert-butyl ester, MS: 255 (M).

[0387] 15.4

[0388] A solution of 257.6 g (982 mmol) triphenylphosphine in 1 l CH₂Cl₂ was treated with 162.8 g (491 mmol) tetrabromomethane (the reaction heated up to reflux and was then cooled with an ice bath) and after 40 min at RT with 157.4 ml (1129 mmol) triethylamine (the reaction heated up to reflux and became dark violet). After cooling (0° C.), 77.96 g (corresponds to 245.5 mmol) of crude trans-(4-Formyl-cyclohexylmethyl)-methyl-carbamic acid tert-butyl

ester in 600 ml CH₂Cl₂ were added during 20 min. The solution was stirred for 20 h at RT, evaporated and filtered through silica gel (deactivated with hexane/0.5% Et₃N) with hexane/Et₂O 99:1 to 4:1 as eluent to yield 61.5 g (61%) of trans-[4-(2,2-Dibromo-vinyl)-cyclohexylmethyl]-methyl-carbamic acid tert-butyl ester, MS: 409 (M, 2Br).

[0389] 15.5

[0390] The following reaction was performed in analogy to the reaction described in: Marshall, James A.; Bartley, Gary S.; Wallace, Eli M. Total Synthesis of the Pseudopteran (-)-Kallolide B, the Enantiomer of Natural (+)-Kallolide B. J. Org. Chem. (1996), 61(17), 5729-5735 and Baker, Raymond; Boyes, Alastair L.; Swain, Christopher J. Synthesis of talaromycins A, B, C, and E. J. Chem. Soc., Perkin Trans. 1 (1990), (5), 1415-21.). A solution of 32.9 g (80 mmol) of trans-[4-(2,2-Dibromo-vinyl)-cyclohexylmethyl]-methyl-carbamic acid tert-butyl ester in 640 ml THF was treated at -78° C. with 105 ml (168 mmol) of BuLi (ca 1.6 M in hexane). After 2 h at this temperature 24 g (800 mmol) of paraformaldehyde were added. The reaction mixture was warmed up to RT for 3 h and after 0.5 h at this temperature extracted with water/Et₂O (3x). The organic phases were washed with aqueous 10% NaCl, dried over Na₂SO₄ and evaporated. Purification by flash-chromatography on silica gel (hexane/EtOAc 9:1 to 2:1) yielded 12.1 g (54%) of trans-[4-(3-Hydroxy-prop-1-ynyl)-cyclohexylmethyl]-methyl-carbamic acid tert-butyl ester, MS: 282 (MH⁺).

[0391] 15.6

[0392] In analogy to example 1.6, trans-[4-(3-Hydroxy-prop-1-ynyl)-cyclohexylmethyl]-methyl-carbamic acid tert-butyl ester was converted to trans-3-(4-Methylaminomethyl-cyclohexyl)-prop-2-yn-1-ol, mp: 97-99° C.; MS: 182 (MH⁺).

[0393] 15.7

[0394] In analogy to example 1.15, trans-3-(4-Methylaminomethyl-cyclohexyl)-prop-2-yn-1-ol with 5.4 eq N-ethyl-diisopropylamine and 1.2 eq 2,5-dibromo-pyrimidine [Brown, Desmond J.; Arantz, B. W., Pyrimidine reactions. XXII. Relative reactivities of corresponding chloro-, bromo-, and iodopyrimidines in aminolysis. J. Chem. Soc. C (1971), Issue 10, 1889-91] yielded, with no NaI after 3 h at 120° C. in the microwave oven, trans-3-(4-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl)-cyclohexyl)-prop-2-yn-1-ol, mp: 121-122° C.; MS: 338 (MH⁺, 1Br).

[0395] 15.8

[0396] In analogy to example 1.26, trans-3-(4-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl)-cyclohexyl)-prop-2-yn-1-ol gave trans-Methanesulfonic acid

3-(4-[(5-bromo-pyrimidin-2-yl)-methyl-amino]-methyl)-cyclohexyl)-prop-2-ynyl ester, MS: 416 (MH⁺, 1Br).

[0397] 15.9

[0398] In analogy to example 1.15, trans-3-(4-Methylaminomethyl-cyclohexyl)-prop-2-yn-1-ol with 5 eq N-ethyl-diisopropylamine and 4 eq 2-chloro-5-ethylpyrimidine gave, with no NaI after 3.75 h at 120° C. in the microwave oven, trans-3-(4-[(5-Ethyl-pyrimidin-2-yl)-methyl-amino]-methyl)-cyclohexyl)-prop-2-yn-1-ol, mp: 69-71° C.; MS: 228 (MH⁺).

[0399] 15.10

[0400] In analogy to example 1.26, trans-3-(4-[(5-Ethyl-pyrimidin-2-yl)-methyl-amino]-methyl)-cyclohexyl)-prop-2-yn-1-ol gave trans-Methanesulfonic acid 3-(4-[(5-ethyl-pyrimidin-2-yl)-methyl-amino]-methyl)-cyclohexyl)-prop-2-ynyl ester, MS: 366 (MH⁺).

[0401] 15.11

[0402] In analogy to example 1.15, trans-3-(4-Methylaminomethyl-cyclohexyl)-prop-2-yn-1-ol with 3.4 eq N-ethyl-diisopropylamine and 4 eq 3,6-dichloropyridazine gave, with no NaI after 30 min at 120-140° C. in the microwave oven, trans-3-(4-[(6-Chloro-pyridazin-3-yl)-methyl-amino]-methyl)-cyclohexyl)-prop-2-yn-1-ol, MS: 294 (MH⁺, 1Cl).

[0403] 15.12

[0404] In analogy to example 1.26, trans-3-(4-[(6-Chloro-pyridazin-3-yl)-methyl-amino]-methyl)-cyclohexyl)-prop-2-yn-1-ol gave trans-Methanesulfonic acid 3-(4-[(6-chloro-pyridazin-3-yl)-methyl-amino]-methyl)-cyclohexyl)-prop-2-ynyl ester, MS: 372 (MH⁺, 1Cl).

Example 16

[0405] A solution of 323 mg (corresponding to 0.49 mmol) of trans-Methanesulfonic acid 3-(4-[(5-bromo-pyrimidin-2-yl)-methyl-amino]-methyl)-cyclohexyl)-prop-2-ynyl ester in 5 ml of methanol was cooled (0° C.), treated with a catalytic amount of NaI, 0.88 ml (4.94 mmol) of Dimethylamine (33% in EtOH 5.6M) and stirred for 16 h at RT. The solvent was evaporated and the residue extracted with aqueous saturated NaHCO₃/Et₂O (3x). The organic phase was dried with Na₂SO₄, filtered and evaporated. Purification by flash column chromatography on silica gel (CH₂Cl₂/MeOH 40:1) gave 137 mg (76%) of pure trans-(5-Bromo-pyrimidin-2-yl)-[4-(3-dimethylamino-prop-1-ynyl)-cyclohexylmethyl]-methyl-amine, mp: 71-72° C.; MS: 365 (MH⁺, 1Br).

[0406] The following compounds were prepared from the corresponding mesylates and secondary amines:

Example	Compound	MS MH ⁺	Mp ° C.	Mesylate	Secondary amine
16.1	trans-2-[[3-(4-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl)-cyclohexyl]-prop-2-ynyl]-ethyl-amino]-ethanol	409, 1Br		trans-Methanesulfonic acid 3-(4-[(5-bromo-pyrimidin-2-yl)-methyl-amino]-methyl)-cyclohexyl)-prop-2-ynyl ester	Ethyl-(2-hydroxy-ethyl)-amine

-continued

Example	Compound	MS MH ⁺	Mp ° C.	Mesylate	Secondary amine
16.2	trans-(5-Bromo-pyrimidin-2-yl)-methyl-[4-(3-piperidin-1-yl-prop-1-ynyl)-cyclohexylmethyl]-amine	391, 1Br		trans-Methanesulfonic acid 3-(4-[[[(5-bromopyrimidin-2-yl)-methyl-amino]-methyl]-cyclohexyl]-prop-2-ynyl ester	Piperidine
16.3	trans-[4-(3-Dimethylamino-prop-1-ynyl)-cyclohexylmethyl]-[5-ethyl-pyrimidin-2-yl)-methyl-amine	315	57- 59	trans-Methanesulfonic acid 3-(4-[[[(5-ethyl-pyrimidin-2-yl)-methyl-amino]-methyl]-cyclohexyl]-prop-2-ynyl ester	Dimethylamine, 33% in EtOH 5.6 M
16.4	trans-2-{Ethyl-[3-(4-[[[(5-ethyl-pyrimidin-2-yl)-methyl-amino]-methyl]-cyclohexyl]-prop-2-ynyl]-amino]-ethanol	359		trans-Methanesulfonic acid 3-(4-[[[(5-ethyl-pyrimidin-2-yl)-methyl-amino]-methyl]-cyclohexyl]-prop-2-ynyl ester	Ethyl-(2-hydroxy-ethyl)-amine
16.5	trans(5-Ethyl-pyrimidin-2-yl)-methyl-[4-(3-piperidin-1-yl-prop-1-ynyl)-cyclohexylmethyl]-amine	355	59- 60	trans-Methanesulfonic acid 3-(4-[[[(5-ethyl-pyrimidin-2-yl)-methyl-amino]-methyl]-cyclohexyl]-prop-2-ynyl ester	Piperidine
16.6	trans-(6-Chloro-pyridazin-3-yl)-[4-(3-dimethylamino-prop-1-ynyl)-cyclohexylmethyl]-methyl-amine	321, 1Cl	81- 82	trans-Methanesulfonic acid 3-(4-[[[(6-chloropyridazin-3-yl)-methyl-amino]-methyl]-cyclohexyl]-prop-2-ynyl ester	Dimethylamine, 33% in EtOH 5.6 M
16.7	trans-2-{[3-(4-[[[(6-Chloro-pyridazin-3-yl)-methyl-amino]-methyl]-cyclohexyl]-prop-2-ynyl]-ethyl-amino]-ethanol	365, 1Cl		trans-Methanesulfonic acid 3-(4-[[[(6-chloropyridazin-3-yl)-methyl-amino]-methyl]-cyclohexyl]-prop-2-ynyl ester	Ethyl-(2-hydroxy-ethyl)-amine
16.8	trans-(6-Chloro-pyridazin-3-yl)-methyl-[4-(3-piperidin-1-yl-prop-1-ynyl)-cyclohexylmethyl]-amine	361, 1Cl	107- 109	trans-Methanesulfonic acid 3-(4-[[[(6-chloropyridazin-3-yl)-methyl-amino]-methyl]-dcyclohexyl]-prop-2-ynyl ester	Piperidine

Example 17

[0407] 17.1

[0408] To a suspension of 50 g (0.33 mol) trans-4-aminocyclohexanol.hydrochloride and 77 g (0.726 mol, 2.2 eq) Na₂CO₃ in 650 ml THF and 150 ml water, 51.2 ml (0.363 mol, 1.1 eq) benzyl chloroformate were added at 5° C. over a period of 20 min. The reaction mixture was stirred at RT for 2 h, diluted with EtOAc and the phases were separated. The organic layer was washed with brine, dried over Na₂SO₄, filtered and evaporated. Trituration from hexane yielded 162.4 g (98%) trans-4-Hydroxy-cyclohexylcarbamic acid benzyl ester as white crystals, MS: 249 (M) (in analogy to: Venuti, Michael C.; Jones, Gordon H.; Alvarez, Robert; Bruno, John J.; J. Med. Chem.; 30; 2; 1987; 303-318).

[0409] 17.2

[0410] To a suspension of 37.9 g (0.94 mol, 2.0 eq) LAH in 1.3 l THF was added a suspension of 117 g (0.47 mol) trans-4-Hydroxy-cyclohexylcarbamic acid benzyl ester in 1 l THF over a period of 6 h via a cannula keeping the

temperature between 5-10° C. The reaction was refluxed over night and a mixture of Na₂SO₄, silica gel and water (160 g, 50 g, 80 ml) was added, stirred for additional 30 min, filtered and concentrated. The crude material was titrated with hexane to yield 27.9 g (46%) trans-4-Methylamino-cyclohexanol. Column chromatography of the mother liquor on silica gel yielded additional 17.1 g (28%) trans-4-Methylamino-cyclohexanol as white solid, MS: 129 (MH⁺) (in analogy to Venuti, Michael C.; Jones, Gordon H.; Alvarez, Robert; Bruno, John J.; J. Med. Chem.; 30; 2; 1987; 303-318).

[0411] 17.3

[0412] In analogy to example 5.4, trans-4-Methylamino-cyclohexanol and 2,5-dibromo-pyrimidine was converted to trans-4-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-cyclohexanol, mp: 140-142° C.; MS: 286 (MH⁺, 1Br).

[0413] 17.4

[0414] A solution of 2.47 g (8.62 mmol) of trans-4-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-cyclohexanol, 5.53 g (25.86 mmol) of trans-1,4-dibromo-2-butene and 0.87 g

(2.57 mmol, 0.3 eq) tetrabutylammoniumhydrogensulfate in 55 ml CH_2Cl_2 were treated with 55 ml of 50% aqueous NaOH. The mixture was stirred at RT for 40 h, 2.76 g (12.93 mmol) of trans-1,4-dibromo-2-butene were added and stirred for further 60 h. Then CH_2Cl_2 was added and the layers were separated. The inorganic layer was extracted with CH_2Cl_2 (3x), the combined organic layers washed with brine and dried over Na_2SO_4 . The residue was purified by column chromatography on silica gel with hexane:EtOAc (9:1 to 2:1) as eluent yielding 0.8 g (22%) trans-(2E)-[4-(4-Bromo-but-2-enyloxy)-cyclohexyl]-(5-bromo-pyrimidin-2-yl)-methyl-amine as light yellow solid, MS: 418 (MH^+ , 2Br).

Example 18

[0415] In analogy to example 2, the following compounds were prepared from the corresponding bromide and secondary amines:

Example	Compound	MS MH+	Bromide	Secondary amine
18.1	trans-(2E)-(5-Bromo-pyrimidin-2-yl)-methyl-[4-(4-piperidin-1-yl-but-2-enyloxy)-cyclohexyl]-amine	423, 1Br	trans-(2E)-[4-(4-Bromo-but-2-enyloxy)-cyclohexyl]-(5-bromo-pyrimidin-2-yl)-methyl-amine	Piperidine
18.2	trans-(2E)-(5-Bromo-pyrimidin-2-yl)-[4-(4-dimethylamino-but-2-enyloxy)-cyclohexyl]-methyl-amine	383, 1Br	trans-(2E)-[4-(4-Bromo-but-2-enyloxy)-cyclohexyl]-(5-bromo-pyrimidin-2-yl)-methyl-amine	Dimethylamine, 33% in EtOH 5.6 M

Example 19

[0416] A solution of 0.2 g (0.7 mmol) of trans-4-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-cyclohexanol and 0.24 g (1.4 mmol) 1-(2-chloroethyl)pyrrolidine hydrochloride in 3.5 ml of DMA was treated at 0° C. with 0.24 g (5.59 mmol) of NaH (55% in oil) in small portions. The reaction was stirred for 30 min at 0° C. After warming up to RT a catalytic amount of NaI was added to the reaction and stirred for 1 h at 80° C. The reaction was cooled and poured into water/Et₂O (3x). The organic phase was dried over Na_2SO_4 evaporated and purified by flash silica gel column (CH_2Cl_2 /MeOH 99:1 to 9:1) to yield 13 g (5%) of trans-(5-Bromo-pyrimidin-2-yl)-methyl-[4-(2-pyrrolidin-1-yl-ethoxy)-cyclohexyl]-amine, MS: 383 (MH^+ , 1Br).

Example 20

[0417] 20.1

[0418] In analogy to example 12, trans-Methanesulfonic acid 4-{2-[(5-bromo-pyrimidin-2-yl)-methyl-amino]-ethyl}-cyclohexylmethyl ester and ethyl-(2-hydroxyethyl)-amine with 1 eq of NaI in DMA at 60° C. for 22 h gave trans-2-[(4-{2-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-ethyl}-cyclohexylmethyl)-ethyl-amino]-ethanol, MS: 399 (MH^+ , 1Br).

[0419] 20.1

[0420] In analogy to example 12, trans-Methanesulfonic acid 4-{2-[(5-bromo-pyrimidin-2-yl)-methyl-amino]-

ethyl}-cyclohexylmethyl ester and 3-amino-1-propanol with 1 eq of NaI in DMA at 60° C. for 46 h gave trans-3-[(4-{2-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-ethyl}-cyclohexylmethyl)-amino]-propan-1-ol, MS: 385 (MH^+ , 1Br).

Example 21

[0421] A solution of 0.21 g (0.6 mmol) trans-3-[(4-{2-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-ethyl}-cyclohexylmethyl)-amino]-propan-1-ol was taken up in 3 ml of dioxan, treated with 3 ml of a aqueous 1N NaH_2PO_4 solution and 3 ml of a 36% aqueous formaldehyde solution (Loibner, H., A. Pruckner, et al. (1984). "Reductive methylation of primary and secondary amines with formaldehyde and phosphorous acid salts." *Tetrahedron Lett.* 25(24): 2535-6). The mixture was heated to 60° C. for 30 min. The mixture was cooled and extracted with 2N NaOH/ether (3x). The organic phase was washed with aqueous 10% NaCl, dried (Na_2SO_4) and evaporated. Purification by flash silica gel column (CH_2Cl_2 /

MeOH 98:2 to 9:1) gave 0.17 g (76%) of trans-3-[(4-{2-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-ethyl}-cyclohexylmethyl)-methyl-amino]-propan-1-ol, MS: 399 (MH^+ , 1Br).

Example 20

[0422] 20.1

[0423] In analogy to example 1.15, trans-3-(4-Methylaminomethyl-cyclohexyl)-prop-2-yn-1-ol with 5.4 eq N-ethyl-diisopropylamine and 1.2 eq 2-chloro-5-n-propylpyrimidine gave, with no NaI after 4 h at 120° C. in the microwave oven, trans-3-(4-{[Methyl-(5-propyl-pyrimidin-2-yl)-amino]-methyl}-cyclohexyl)-prop-2-yn-1-ol, mp: 78-79° C.; MS: 302 (MH^+).

[0424] 22.2

[0425] In analogy to example 1.26, trans-3-(4-{[Methyl-(5-propyl-pyrimidin-2-yl)-amino]-methyl}-cyclohexyl)-prop-2-yn-1-ol gave trans-Methanesulfonic acid 3-(4-{[methyl-(5-propyl-pyrimidin-2-yl)-amino]-methyl}-cyclohexyl)-prop-2-ynyl ester, MS: 380 (MH^+).

[0426] 22.3

[0427] In analogy to example 1.15, trans-3-(4-Methylaminomethyl-cyclohexyl)-prop-2-yn-1-ol with 5.4 eq N-ethyl-diisopropylamine and 1.2 eq 2-bromo-5-chloro-pyrimidine [synthesized from 5-chloro-2-hydroxy-pyrimidine in analogy to Brown, Desmond J.; Arantz, B. W., Pyrimidine reactions. XXII. Relative reactivities of corresponding chloro-, bromo-, and iodopyrimidines in aminolysis. J.

Chem. Soc. C (1971), Issue 10, 1889-91] gave, with no NaI after 2 h at 120° C. in the microwave oven, trans-3-(4-[[[(5-Chloro-pyrimidin-2-yl)-methyl-amino]-methyl]-cyclohexyl]-prop-2-yn-1-ol, mp: 108-110° C.; MS: 294 (MH⁺, 1Cl).

[0428] 22.4

[0429] In analogy to example 1.26, trans-3-(4-[[[(5-Chloro-pyrimidin-2-yl)-methyl-amino]-methyl]-cyclohexyl]-prop-2-yn-1-ol gave trans-Methanesulfonic acid 3-(4-[[[(5-chloro-pyrimidin-2-yl)-methyl-amino]-methyl]-cyclohexyl]-prop-2-ynyl ester, MS: 372 (MH⁺, 1Cl).

Example 23

[0430] 23.1

[0431] In analogy to example 16, trans-Methanesulfonic acid 3-(4-[[methyl-(5-propyl-pyrimidin-2-yl)-amino]-methyl]-cyclohexyl)-prop-2-ynyl ester and Dimethylamine (33% in EtOH 5.6M) in DMA gave trans-[4-(3-Dimethylamino-prop-1-ynyl)-cyclohexylmethyl]-methyl-(5-propyl-pyrimidin-2-yl)-amine, mp: 49-50° C.; MS: 329 (MH⁺).

[0432] The following compounds were prepared from the corresponding mesylates and secondary amines:

Example	Compound	MS MH ⁺	Mp ° C.	Mesylate	Secondary amine
23.2	trans-2-{Ethyl-[3-(4-[[methyl-(5-propyl-pyrimidin-2-yl)-amino]-methyl]-cyclohexyl)-prop-2-ynyl]-amino}-ethanol	373	<30	trans-Methanesulfonic acid 3-(4-[[methyl-(5-propyl-pyrimidin-2-yl)-amino]-methyl]-cyclohexyl)-prop-2-ynyl ester	Ethyl-(2-hydroxy-ethyl)-amine
23.3	trans-(5-Chloro-pyrimidin-2-yl)-[4-(3-dimethylamino-prop-1-ynyl)-cyclohexylmethyl]-methyl-amine	321, 1Cl	74-75	trans-Methanesulfonic acid 3-(4-[[[(5-chloro-pyrimidin-2-yl)-methyl-amino]-methyl]-cyclohexyl]-prop-2-ynyl ester	Dimethylamine, 33% in EtOH 5.6 M
23.4	trans-2-{[3-(4-[[[(5-Chloro-pyrimidin-2-yl)-methyl-amino]-methyl]-cyclohexyl]-prop-2-ynyl]-ethyl-amino]-ethanol	365, 1Cl		trans-Methanesulfonic acid 3-(4-[[[(5-chloro-pyrimidin-2-yl)-methyl-amino]-methyl]-cyclohexyl]-prop-2-ynyl ester	Ethyl-(2-hydroxy-ethyl)-amine

EXAMPLES

Example A

[0433] Film coated tablets containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per tablet	
<u>Kernel:</u>		
Compound of formula (I)	10.0 mg	200.0 mg
Microcrystalline cellulose	23.5 mg	43.5 mg
Lactose hydrous	60.0 mg	70.0 mg
Povidone K30	12.5 mg	15.0 mg

-continued

Ingredients	Per tablet	
Sodium starch glycolate	12.5 mg	17.0 mg
Magnesium stearate	1.5 mg	4.5 mg
(Kernel Weight)	120.0 mg	350.0 mg
Film Coat:		
Hydroxypropyl methyl cellulose	3.5 mg	7.0 mg
Polyethylene glycol 6000	0.8 mg	1.6 mg
Talc	1.3 mg	2.6 mg
Iron oxide (yellow)	0.8 mg	1.6 mg
Titan dioxide	0.8 mg	1.6 mg

[0434] The active ingredient is sieved and mixed with microcrystalline cellulose and the mixture is granulated with a solution of polyvinylpyrrolidone in water. The granulate is mixed with sodium starch glycolate and magnesium stearate and compressed to yield kernels of 120 or 350 mg respectively. The kernels are lacquered with an aqueous solution/suspension of the above mentioned film coat.

Example B

[0435] Capsules containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per capsule
Compound of formula (I)	25.0 mg
Lactose	150.0 mg
Maize starch	20.0 mg
Talc	5.0 mg

[0436] The components are sieved and mixed and filled into capsules of size 2.

Example C

[0437] Injection solutions can have the following composition:

Compound of formula (I)	3.0 mg
Polyethylene Glycol 400	150.0 mg
Acetic Acid	q.s. ad pH 5.0
Water for injection solutions	ad 1.0 ml

[0438] The active ingredient is dissolved in a mixture of Polyethylene Glycol 400 and water for injection (part). The pH is adjusted to 5.0 by Acetic Acid. The volume is adjusted to 1.0 ml by addition of the residual amount of water. The solution is filtered, filled into vials using an appropriate overage and sterilized.

Example D

[0439] Soft gelatin capsules containing the following ingredients can be manufactured in a conventional manner:

<u>Capsule contents:</u>	
Compound of formula (I)	5.0 mg
Yellow wax	8.0 mg
Hydrogenated Soya bean oil	8.0 mg
Partially hydrogenated plant oils	34.0 mg
Soya bean oil	110.0 mg
Weight of capsule contents	165.0 mg
<u>Gelatin capsule</u>	
Gelatin	75.0 mg
Glycerol 85%	32.0 mg
Karion 83	8.0 mg (dry matter)
Titan dioxide	0.4 mg
Iron oxide yellow	1.1 mg

[0440] The active ingredient is dissolved in a warm melting of the other ingredients and the mixture is filled into soft gelatin capsules of appropriate size. The filled soft gelatin capsules are treated according to the usual procedures.

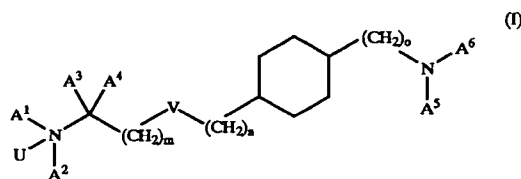
Example E

[0441] Sachets containing the following ingredients can be manufactured in a conventional manner:

Compound of formula (I)	50.0 mg
Lactose, fine powder	1015.0 mg
Microcrystalline cellulose (AVICEL PH 102)	1400.0 mg
Sodium carboxymethyl cellulose	14.0 mg
Polyvinylpyrrolidon K 30	10.0 mg
Magnesiumstearate	10.0 mg
Flavoring additives	1.0 mg

[0442] The active ingredient is mixed with lactose, microcrystalline cellulose and sodium carboxymethyl cellulose and granulated with a mixture of polyvinylpyrrolidon in water. The granulate is mixed with magnesiumstearate and the flavouring additives and filled into sachets.

1. A compound of the formula



wherein

U is O or a lone pair,

V is a single bond, O, S, $-\text{CH}=\text{CH}-\text{CH}_2-\text{O}-$, $-\text{CH}=\text{CH}-$, or $-\text{C}=\text{C}-$,

m and n independently from each other are 0 to 7 and m+n is 0 to 7, with the proviso that m is not 0 if V is O or S,

o is 0 to 2

A¹ is hydrogen, lower-alkyl, hydroxy-lower-alkyl, or lower-alkenyl,

A² is lower-alkyl, cycloalkyl, cycloalkyl-lower-alkyl, or lower-alkenyl, optionally substituted by R¹, or

A¹ and A² are bonded to each other to form a ring and -A¹-A²- is lower-alkylene or lower-alkenylene, optionally substituted by R¹, in which one $-\text{CH}_2-$ group of -A¹-A²- can optionally be replaced by NR², S, or O,

A³ and A⁴ independently from each other are hydrogen or lower-alkyl, or

A³ and A⁴ are bonded to each other to form a ring together with the carbon atom to which they are attached and -A³-A⁴- is $-(\text{CH}_2)_{2-5}-$,

A⁵ is hydrogen, lower-alkyl, or lower-alkenyl,

A⁶ is pyridinyl, pyridazinyl, pyrimidinyl or pyrazinyl, optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower-alkyl, lower-alkyl-cycloalkyl, thio-lower-alkoxy, cycloalkyl, carbamoyl, carboxy, carboxy-lower-alkyl, cyano, amino, mono- and dialkylamino, lower-alkoxy, lower-alkoxy-lower-alkyl, lower-alkoxy-carbonyl, lower-alkoxy-carbonyl-lower-alkyl, lower-alkenyl, lower-alkynyl, aryl, aryl-lower-alkyl, aryloxy, halogen, heteroaryl, heterocyclyl, heterocyclyl-lower-alkyl and trifluoromethyl,

R¹ is hydroxy, hydroxy-lower-alkyl, lower-alkoxy, lower-alkoxycarbonyl, halogen, CN, N(R³, R⁴), or thio-lower-alkoxy,

R², R³, and R⁴ independently from each other are hydrogen or lower-alkyl,

and pharmaceutically acceptable salts thereof, with the proviso, that the compound of formula (I) is not trans-[4-(2-Dipropylamino-ethyl)-cyclohexyl]-pyrimidin-2-yl-amine.

2. The compound according to claim 1, wherein U is a lone pair.

3. The compound according to claim 1, wherein V is a single bond.

4. The compound according to claim 1 wherein V is O.
5. The compound according to claim 1 wherein V is S.
6. The compound according to claim 1 wherein V is $\text{—CH=CH—CH}_2\text{—O—}$.
7. The compound according to claim 1 wherein V is —CH=CH— .
8. The compound according to claim 1 wherein V is —C=C— .
9. The compound according to claim 1, wherein A⁶ is the substituted or unsubstituted pyridinyl.
10. The compound according to claim 1, wherein A⁶ is the substituted or unsubstituted pyridazinyl.
11. The compound according to claim 10, wherein A⁶ is 6-chloro-pyridazin-3-yl.
12. The compound according to claim 1, wherein A⁶ is the substituted or unsubstituted pyrimidinyl.
13. The compound according to claim 11, wherein A⁶ is 5-bromo-pyrimidin-2-yl, 5-chloro-pyrimidin-2-yl, 5-pyridin-4-yl-pyrimidin-2-yl, 5-ethyl-pyrimidin-2-yl.
14. The compound according to claim 1, wherein A⁶ is the substituted or unsubstituted pyrazinyl.
15. The compound according to claim 1, wherein m is 0 to 3.
16. The compound according to claim 1, wherein m is 0.
17. The compound according to claim 1, wherein n is 0 to 1.
18. The compound according to claim 1, wherein n is 0.
19. The compound according to claim 1, wherein o is 0 or 1.
20. The compound according to claim 1, wherein A¹ is lower-alkyl.
21. The compound according to claim 1, wherein A¹ is methyl or ethyl.
22. The compound according to claim 1, wherein A² is lower-alkenyl, or lower-alkyl optionally substituted by R², wherein R² is hydroxy or lower-alkoxy.
23. The compound according to claim 1, wherein A² is methyl, propyl or 2-hydroxy-ethyl.
24. The compound according to claim 1, wherein A¹ and A² are bonded to each other to form a ring and -A¹-A²- is lower-alkylene.
25. The compound according to claim 24, wherein -A¹-A²- is $\text{—(CH}_2\text{)}_5\text{—}$.
26. The compound according to claim 1, wherein A³ and A⁴ are hydrogen.
27. The compound according to claim 1, wherein A⁵ is hydrogen or lower-alkyl.
28. The compound according to claim 1, wherein A⁵ is methyl.
29. The compound according to claim 1, wherein A⁶ is pyridinyl, pyridazinyl, pyrimidinyl or pyrazinyl, optionally substituted with 1 or 2 substituents independently selected from the group consisting of lower-alkyl, lower-alkoxy, halogen, pyridyl and thienyl.

30. The compound according to claim 1, wherein A⁶ is pyridazinyl or pyrimidinyl, optionally substituted with 1 or 2 substituents independently selected from the group consisting of bromo, chloro, ethyl and pyridyl.

31. The compound according to claim 1, wherein A⁶ is 5-bromo-pyrimidin-2-yl, 6-chloro-pyridazin-3-yl, 5-chloro-pyrimidin-2-yl, 5-pyridin-4-yl-pyrimidin-2-yl, 5-ethyl-pyrimidin-2-yl.

32. A compound selected from the group consisting of

- trans-(5-Bromo-pyrimidin-2-yl)-methyl-{4-[3-(methyl-propyl-amino)-prop-1-ynyl]-cyclohexyl}-amine,
- trans-(5-Bromo-pyrimidin-2-yl)-[4-(3-dimethylamino-prop-1-ynyl)-cyclohexyl]-methyl-amine,
- trans-(5-Chloro-pyrimidin-2-yl)-[4-(3-dimethylamino-prop-1-ynyl)-cyclohexyl]-methyl-amine,
- trans-[(5-Bromo-pyrimidin-2-yl)-methyl-4-(3-piperidin-1-yl-prop-1-ynyl)-cyclohexyl]-amine],
- trans-[4-(3-Dimethylamino-prop-1-ynyl)-cyclohexyl]-methyl-(5-pyridin-4-yl-pyrimidin-2-yl)-amine,
- trans-[4-(3-Dimethylamino-prop-1-ynyl)-cyclohexyl]-(5-ethyl-pyrimidin-2-yl)-methyl-amine,
- trans-(5-Bromo-pyrimidin-2-yl)-[4-(3-dimethylamino-prop-1-ynyl)-cyclohexylmethyl]-methyl-amine,
- trans-2-{[3-(4-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl)-cyclohexyl]-prop-2-ynyl}-ethyl-amino}-ethanol,
- trans-2-{Ethyl-[3-(4-[(5-ethyl-pyrimidin-2-yl)-methyl-amino]-methyl)-cyclohexyl]-prop-2-ynyl]-amino}-ethanol,
- trans(5-Ethyl-pyrimidin-2-yl)-methyl-[4-(3-piperidin-1-yl-prop-1-ynyl)-cyclohexylmethyl]-amine,

and pharmaceutically acceptable salts thereof.

33. A compound selected from the group consisting of trans-2-{[3-(4-[(6-Chloro-pyridazin-3-yl)-methyl-amino]-methyl)-cyclohexyl]-prop-2-ynyl}-ethyl-amino}-ethanol, and trans-(6-Chloro-pyridazin-3-yl)-[4-(3-dimethylamino-prop-1-ynyl)-cyclohexyl]-methyl-amine, and the pharmaceutically acceptable salts thereof.

34. A pharmaceutical composition for regulating cholesterol biosynthesis comprising a pharmacologically effective amount of the compound according to claim 1 and a pharmaceutically acceptable carrier and/or adjuvant.

35. A method for the treatment or prophylaxis of diseases associated with high levels of cholesterol biosynthesis comprising administering a composition in accordance with claim 34 to reduce cholesterol biosynthesis.

* * * * *

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The United States Patent and Trademark Office (Office or USPTO) plans in the near future to: (1) cease mailing copies of U.S. patents and U.S. patent application publications (US patent references) with Office actions except for citations made during the international stage of an international application under the Patent Cooperation Treaty and those made during reexamination proceedings; and (2) provide electronic access to, with convenient downloading capability of, the US patent references cited in an Office action via the Office's private Patent Application Information Retrieval (PAIR) system which has a new feature called "E-Patent Reference." Before ceasing to provide copies of U.S. patent references with Office actions, the Office shall test the feasibility of the E-Patent Reference feature by conducting a two-month pilot project starting with Office actions mailed after December 1, 2003. The Office shall evaluate the pilot project and publish the results in a notice which will be posted on the Office's web site (www.USPTO.gov) and in the Patent Official Gazette (O.G.). In order to use the new E-Patent Reference feature during the pilot period, or when the Office ceases to send copies of U.S. patent references with Office actions, the applicant must: (1) obtain a digital certificate from the Office; (2) obtain a customer number from the Office, and (3) properly associate applications with the customer number. The pilot project does not involve or affect the current Office practice of supplying paper copies of foreign patent documents and non-patent literature with Office actions. Paper copies of references will continue to be provided by the USPTO for searches and written opinions prepared by the USPTO for international applications during the international stage and for reexamination proceedings.

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Access to private PAIR is required to utilize E-Patent Reference. If you don't already have access to private PAIR, the Office urges practitioners, and applicants not represented by a practitioner, to take advantage of the transition period to obtain a no-cost USPTO Public Key Infrastructure (PKI) digital certificate, obtain a USPTO customer number, associate all of their pending and new application filings with their customer number, install no-cost software (supplied by the Office) required to access private PAIR and E-Patent Reference feature, and make appropriate arrangements for Internet access. The full instructions for obtaining a PKI digital certificate are available at the Office's Electronic Business Center (EBC) web page at: <http://www.uspto.gov/ebc/downloads.html>. Note that a notarized signature will be required to obtain a digital certificate.

To get a Customer Number, download and complete the Customer Number Request form, PTO-SB125, at: <http://www.uspto.gov/web/forms/sb0125.pdf>. The completed form can then be transmitted by facsimile to the Electronic Business Center at (703) 308-2840, or mailed to the address on the form. If you are a registered attorney or patent agent, then your registration number must be associated with your customer number. This is accomplished by adding your registration number to the Customer Number Request form. A description of associating a customer number with an application is described at the EBC web page at: http://www.uspto.gov/ebc/registration_pair.html.

The E-Patent Reference feature will be accessed using a new button on the private PAIR screen. Ordinarily all of the cited U.S. patent and U.S. patent application publication references will be available over the Internet using the Office's new E-Patent Reference feature. The size of the references to be downloaded will be displayed by E-Patent Reference so the download time can be estimated. Applicants and registered practitioners can select to download all of the references or any combination of cited references. Selected references will be downloaded as complete documents as Adobe Portable Document Format (.pdf) files. For a limited period of time, the USPTO will include a copy of this notice with Office actions to encourage applicants to use this new feature and, if needed, to take the steps outlined above in order to be able to utilize this new feature during the pilot and thereafter.

During the two-month pilot, the Office will evaluate the stability and capacity of the E-Patent Reference feature to reliably provide electronic access to cited U.S. patent and U.S. patent application publication references. While copies of U.S. patent and U.S. patent application publication references cited by examiners will continue to be mailed with Office actions during the pilot project, applicants are encouraged to use the private PAIR and the E-Patent Reference feature to electronically access and download cited U.S. patent and U.S. patent application publication references so the Office will be able to objectively evaluate its performance. The public is encouraged to submit comments to the Office on the usability and performance of the E-Patent Reference feature during the pilot. Further, during the pilot period registered practitioners, and applicants not represented by a practitioner, are encouraged to experiment with the feature, develop a proficiency in using the feature, and establish new internal processes for using the new access to the cited U.S. patents and U.S. patent application publications to prepare for the anticipated cessation of the current Office practice of supplying copies of such cited

references. The Office plans to continue to provide access to the E-Patent Reference feature during its evaluation of the pilot.

Comments

Comments concerning the E-Patent Reference feature should be in writing and directed to the Electronic Business Center (EBC) at the USPTO by electronic mail at eReference@uspto.gov or by facsimile to (703) 308-2840. Comments will be posted and made available for public inspection. To ensure that comments are considered in the evaluation of the pilot project, comments should be submitted in writing by January 15, 2004.

Comments with respect to specific applications should be sent to the Technology Centers' customer service centers. Comments concerning digital certificates, customer numbers, and associating customer numbers with applications should be sent to the Electronic Business Center (EBC) at the USPTO by facsimile at (703) 308-2840 or by e-mail at EBC@uspto.gov.

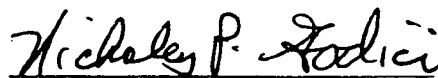
Implementation after Pilot

After the pilot, its evaluation, and publication of a subsequent notice as indicated above, the Office expects to implement its plan to cease mailing paper copies of U.S. patent references cited during examination of non provisional applications on or after February 2, 2004; although copies of cited foreign patent documents, as well as non-patent literature, will still be mailed to the applicant until such time as substantially all applications have been scanned into IFW.

For Further Information Contact

Technical information on the operation of the IFW system can be found on the USPTO website at <http://www.uspto.gov/web/patents/ifw/index.html>. Comments concerning the E-Patent Reference feature and questions concerning the operation of the PAIR system should be directed to the EBC at the USPTO at (866) 217-9197. The EBC may also be contacted by facsimile at (703) 308-2840 or by e-mail at EBC@uspto.gov.

Date. 12/1/03



Nicholas P. Godici
Commissioner for Patents